THE MODE OF ACTION OF CHLOROTHIAZIDE IN HYPERTENSION: WITH SPECIAL REFERENCE TO POTENTIATION OF GANGLION-BLOCKING AGENTS

C. T. DOLLERY
B.Sc., M.B. Birm., M.R.C.P.
MEDICAL REGISTRAR

M. HARINGTON
M.B. Cantab., M.R.C.P.
SENIOR MEDICAL REGISTRAR AND TUTOR

G. KAUFMANN
M.D. Zürich
RESEARCH ASSISTANT

DEPARTMENT OF MEDICINE,
POSTGRADUATE MEDICAL SCHOOL OF LONDON, W.12

CHLOROTHIAZIDE is a powerful diuretic agent which was synthesised by Novello and Sprague (1957). Several workers have reported that this drug potentiates the hypotensive effects of ganglion-blocking agents (Tapia et al. 1957, Heider et al. 1958). There has been less agreement about the action of chlorothiazide alone, some finding a significant pressure-lowering effect (Freis et al. 1958, Wilkins et al. 1958, Hall and Owen 1959) and others little or none (Heider et el. 1958, Winer 1958).

The pharmacological basis of the hypotensive action of chlorothiazide has been disputed. It seems natural to suppose that it might depend on sodium depletion. Freis et al. (1958) believe that the principal action of chlorothiazide is to bring about a reduction in plasma-volume; but Winer (1958) was unable to demonstrate a significant change in plasma-volume. Wilkins et al. (1958) found some reduction of blood-pressure after chlorothiazide alone, and speculated that the hypotensive action might depend partly upon interference with a renal pressor substance.

Our study was designed to investigate the action on the blood-pressure of chlorothiazide, both alone and in conjunction with ganglion-blocking drugs. Two series of observations were made—(1) on the acute effects of intravenous injection of chlorothiazide, and (2) on the effects of several days' chlorothiazide therapy under standard conditions. Preliminary studies suggested that the greatest potentiation of ganglion blockade was associated with a significant increase in the packed-cell volume. We therefore studied the relation of changes in plasma-volume and sodium balance to the presence or absence of a hypotensive effect in patients on chlorothiazide. Particular attention was paid to postural changes in blood-pressure in the assessment of hypotensive action.

Methods

The patients studied after single intravenous doses of chlorothiazide were hypertensives without heart-failure. They had a normal uncontrolled sodium intake from the ward diet. One group was given an intravenous injection of chlorothiazide 0·5 g., and the blood-pressure response was observed. In a second group the sensitivity to intravenous pentolinium (see below) was assessed on 2 successive days; on the 2nd day chlorothiazide 0·5–1·0 g. was given intravenously within the 2-hour period before the pentolinium injection.

The patients for the longer-term study were all hypertensives with a blood-pressure over 200/100 mm. Hg when first seen. None had had hypotensive treatment, and none had a history of heart-failure. Thirteen patients were studied, of whom four had retinitis, and the remainder had retinal arterial thickening only. Patients were not excluded because of renal disease, but none had a blood-urea over 45 mg. per 100 ml. when the study began.

The patients were admitted to a metabolic ward, and given a diet containing 22 mEq. of sodium daily. Supplements raised the sodium intake to 72 mEq. daily. This diet corresponded approximately to the sodium intake on a " no added salt " regime. The sodium intake was accurately known, and the supplements were not so great as to cause nausea and vomiting. The sodium intake being only slightly restricted, equilibration was rapid and the effect of the diet alone negligible. In 6 cases the potassium intake was controlled at 80 mEq. daily. Fluid intake was not restricted.

The urine was collected in 24-hour batches, and analysed for total sodium and, where appropriate, potassium. Patients were weighed daily, and the blood-pressure was recorded in the lying and standing position four times daily. After 3 days on the diet, the sensitivity to intravenous pentolinium was determined. Next morning the plasma-volume was measured, and blood was taken for the determination of hæmoglobin and packed-cell volume, and for serum sodium, potassium, chloride, bicarbonate, and urea levels. For the next 4 days chlorothiazide 1 g. was given orally at 10 A.M. and 6 P.M. On the 3rd day of chlorothiazide the sensitivity to pentolinium was estimated again, at the same time as before. Next morning the plasma-volume, hæmoglobin, and packed-cell volume, and the serum-electrolytes were again determined.

If the plasma-volume fell during the period on chlorothiazide the deficit was made good by the infusion of an equal volume of 6% salt-free dextran. 30 minutes after infusion the sensitivity to pentolinium was assessed again.

Techniques

Sensitivity to Pentolinium

The blood-pressure was measured with a standard sphygmomanometer, first with the patient standing, and then when lying flat in bed with the head on one pillow. Readings were taken every 2 minutes until a steady level was reached. At this point an intravenous injection of pentolinium 2·5 mg. was given, and for 15 minutes the pressure was measured every minute. At the end of that time it was taken with the patient sitting and standing. These data gave five standard values—the initial standing and lying pressures, the pressure just before injection of pentolinium, and the pressures after sitting up and after 1 minute's standing at the end of the test.

The constancy of the hypotensive response to a standard intravenous dose of pentolinium was assessed in another series of hypertensive subjects. The drug was given to five patients on 4 successive days, and under these conditions the same dose produced a similar fall in blood-pressure in the same patient from day to day. Any variation would be expected to be in the direction of development of tolerance to the drug, but no such effect was observed with single daily doses over this period.

Plasma-volume

All estimations were done with the patient fasting at 9 A.M. The dye T 1824 was used as the indicator substance at a dilution of 1 mg. per ml. After withdrawal of blood for a blank estimation, the dye was injected intravenously from a 20 ml. syringe calibrated by weight. Blood samples were withdrawn from the opposite arm 10 and 15 minutes after injection. The dye was extracted from the plasma by the method of Campbell et al. (1958), and its concentration was measured on a 'Unicam' spectrophotometer at 615 mμ. The plasma-volume was calculated by extrapolation back to zero time, assuming a continuous loss of 10% of the dye from the circulation during the 1st hour after injection (Mollison 1956).

Dextran infusion.—Dextran solutions of a molecular weight of about 75,000 make a reliable plasma-volume expander (Bull

et al. 1949). In these studies we used a 6% salt-free solution of dextran ('Dextraven'). This has the advantage that no sodium is infused, and the effect can be judged solely from the standpoint of volume change. No adverse reactions of any kind were observed during or after the infusions.

Hæmoglobin and packed-cell volume, and serum sodium, potassium, chloride, bicarbonate, and urea were determined by standard laboratory methods.

Results

ACUTE EFFECTS OF INTRAVENOUS CHLOROTHIAZIDE

Single intravenous doses of chlorothiazide 0·5 g. given to three patients had no effect on the blood-pressure measured at intervals of ½–1 hour for 6 hours, when the patient was lying or standing. In four other patients the response to a standard dose of pentolinium was not altered within 2 hours of an intravenous dose of 0·5–1·0 g. of chlorothiazide. Since chlorothiazide is very rapidly excreted after intravenous injection—at least in the dog (Beyer 1958)—this negative result suggests that increased hypotension after chlorothiazide is not a direct pharmacological action of the drug itself.

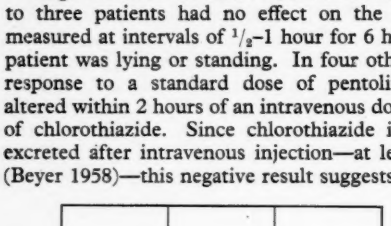


Fig. 1—Plasma-volume before and after 3 days' treatment with chlorothiazide in hypertensive patients (a) without change in sensitivity to pentolinium, (b) with increased sensitivity, and (c) with postural hypotension and increased sensitivity to pentolinium.

EFFECTS OF CONTINUED TREATMENT WITH CHLOROTHIAZIDE

After 3 days' treatment with chlorothiazide nine of the thirteen patients in this group had an increased sensitivity to pentolinium in terms of the blood-pressure response. No change was observed in the other four. The effects of chlorothiazide are analysed in detail below.

Plasma-volume

The initial values for plasma-volume all lay within the normal range of 40 to 60 ml. per kg. (fig. 1). There was a fall in plasma-volume in eight patients, all of whom developed an increased hypotensive response to pentolinium. Five had no measurable fall in plasma-volume, but only one of these became more sensitive to pentolinium. Two controls who had no chlorothiazide had a small fall in plasma-volume on the diet alone, without alteration in their response to pentolinium.

All the patients with an alteration of plasma-volume as measured by the dye method had also a reciprocal change in the packed-cell volume. Care was taken that the blood withdrawn for estimation came from unobstructed veins. There was agreement between the change in plasma-volume and packed-cell volume in both direction and magnitude (see table).

Of the eight patients whose plasma-volume fell, seven were infused with a volume of dextran equal to the calculated fall. In six of these the sensitivity to pentolinium returned to about the pre-chlorothiazide level. Fig. 2 shows a typical response.

EFFECTS OF 3 DAYS' TREATMENT WITH CHLOROTHIAZIDE

Case no.	Plasma-volume (ml.)		Packed-cell volume (%)		Cumulative sodium balance (mEq.)	% change in plasma-volume
	Initial	After 3 days' chlorothiazide	Initial	After 3 days' chlorothiazide		
1	1770	1920	41	37	+64	+8·5
2	3300	2400	45	49	−188	−27·3
3	2210	2000	45	46	−89	−10·0
4	3390	3030	42	44	−148	−10·6
5	1910	2070	42	40·5	−187	+6·6
6	3040	2480	40	43·5	−146	−14·5
7	1980	1800	35	40	−81	−9·2
8	2520	2002	45	46	−263	−16·1
9	2870	2600	38·5	43	−277	−9·7
10	2790	2850	44	43	+6	+2·0
11	3430	2840	47	51	−184	−17·2
12	2880	2740	45	45	−158	−4·9
13	2370	2380	..	..	−292	0·0

Diuresis and Weight Loss

The volume of urine was increased on the 1st day of chlorothiazide, an extra 1·0–1·5 litres being passed. Thereafter the diuresis subsided and by the 3rd day the urinary volume had returned to normal. During the period of study all the patients lost weight, in amounts ranging from 0·3 to 2·25 kg. The largest decreases in weight were associated with the greatest diureses.

Sodium Balance

Eleven of the thirteen patients were in negative sodium balance after 3 days' treatment with chlorothiazide. The loss of sodium ranged from 292 to 81 mEq. For comparative purposes the negative sodium balance has been expressed as mEq. of sodium lost per kg. body-weight at the beginning of the study, and the results ranged from 5·1 to 1·3 mEq. per kg., with a mean of 2·8 mEq. per kg. Eight of the eleven patients who lost sodium also had a fall in plasma-volume, and they became more sensitive to pentolinium. In three patients there was no change in plasma-volume despite substantial sodium loss; two of them did not become more sensitive to pentolinium, and the one who did had the largest negative sodium balance in this study.

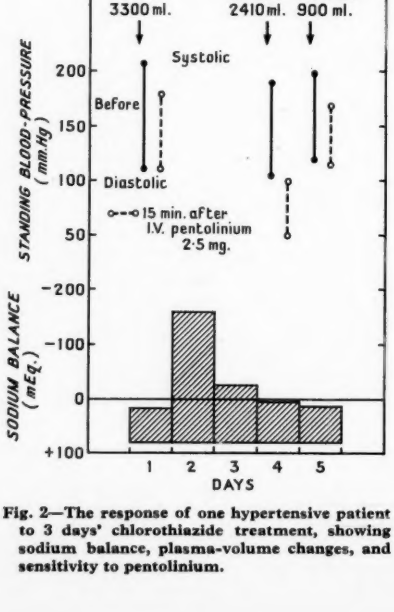


Fig. 2—The response of one hypertensive patient to 3 days' chlorothiazide treatment, showing sodium balance, plasma-volume changes, and sensitivity to pentolinium.

The serum-sodium level fell slightly by a mean of 4·1 mEq. per litre and the chloride level showed the same trend.

The table gives the

sodium balance figures and the plasma-volume changes in all the patients. Fig. 2 shows the blood-pressure responses, plasma-volumes, and sodium balance in a typical patient. It illustrates that the largest loss of sodium is on the 1st day of treatment with chlorothiazide, and that by the 3rd day the sodium output is again in balance with the intake. This pattern was seen in all the patients who had a natriuresis.

Potassium Metabolism

The serum-potassium level fell in all the patients except one who had oliguria after taking chlorothiazide. The average fall was 0·68 mEq. per litre, with a range of 0·2–1·5 mEq. per litre. In six cases where the potassium balance was measured the mean potassium loss during the 3 days was 46 mEq., with a range of 26–97 mEq.

Blood-urea

The blood-urea rose in all except one case. The rise was usually small, with a mean of 10 mg. per 100 ml., and a range of −4 to +23 mg. per 100 ml. In another case there was a greater rise in the blood-urea from 51 to 126 mg. per 100 ml., associated with oliguria.

Daily Blood-pressure Records

The casual blood-pressure records of most patients fell during their stay in hospital. The average of the daily pressures was taken to decide whether there had been a change during the period on chlorothiazide. There was no significant change attributabe to the drug in six patients. These included all four who had not shown an increased response to pentolinium. In five patients on chlorothiazide there was a slight fall in the casual records, and in two a slight rise.

Four patients developed postural hypotension while on chlorothiazide. One had had a thoracolumbar sympathectomy 10 years before. Another had previously had some postural fall in pressure, but this was increased when chlorothiazide was given. In all four there was a significant fall in plasma-volume (fig. 1c).

Discussion

From our results certain conclusions may be drawn about the action of chlorothiazide in modifying the response of the blood-pressure to ganglion-blocking agents, as exemplified by pentolinium. First, it is unlikely that chlorothiazide has any direct hypotensive action per se, since no change in blood-pressure nor potentiation of ganglion blockade was observed after intravenous injection of large single doses. Although Wilkins et al. (1958) reported a lowering of blood-pressure within a few hours of the first dose of chlorothiazide, in our experience, when patients were tested daily with a standard dose of pentolinium, there was no increase of sensitivity to the drug until the 2nd day after starting chlorothiazide, and it was maximal on the 3rd or 4th day. (With the non-quaternary ganglion-blocking drugs, such as mecamylamine, the situation is different, the effect of chlorothiazide being seen earlier, as discussed below.)

The action of chlorothiazide under investigation therefore appears to be cumulative. It seemed reasonable at first to relate this to the powerful effect of the drug in causing loss of sodium, particularly as dietary sodium restriction enhances the hypotensive action of ganglion-blocking drugs, such as hexamethonium (Restall and Smirk 1950). A negative sodium balance was observed in eleven of our patients, but the extent of this did not correlate well with the development of increased sensitivity to pentolinium. There was better correlation with the figures for the accompanying changes in plasma-volume.

In eight of the thirteen patients studied, 3 days' treatment with chlorothiazide produced a fall in plasma-volume (mean 14%), and all of them showed increased sensitivity to pentolinium. In four out of five in whom there was no significant change in plasma-volume the effect of pentolinium was unchanged. Replacement of the calculated loss in plasma-volume with salt-free dextran in seven patients was followed by reduction in sensitivity to pentolinium to about the pre-chlorothiazide level in all except one. These results suggest that the increased sensitivity to pentolinium which develops in patients on chlorothiazide can be accounted for mainly by the fall in plasma-volume rather than by the direct result of sodium depletion, though if the latter is very great it also may play a part.

The potentiating effect of chlorothiazide on pentolinium particularly affected the postural fall of blood-pressure. Some postural hypotension was observed also as a response to chlorothiazide itself, apart from the test dose of pentolinium, in four of the thirteen patients. Three of these had a considerable fall in plasma-volume, while the fourth was the patient who had previously had an extensive sympathectomy. The postural hypotensive response was abolished in each case by the infusion of sufficient dextran to replace the lost plasma-volume.

That a reduction in plasma-volume is the principal factor leading to an increased sensitivity to ganglion-blocking drugs, and sometimes to the development of postural hypotension, in patients treated with chlorothiazide is corroborated by the work of O'Donnell (cited by Smirk 1957). He showed that in patients on strict dietary sodium restriction, postural hypotension was closely related to a reduction in the plasma-volume; and he found that the postural fall in pressure could be abolished by infusion of salt-free dextran. O'Donnell observed also that the increased postural sensitivity to ganglion-blocking drugs in patients on a salt-free diet correlated with a diminution in plasma-volume, and he confirmed a report of Freis et al. (1951) that the extent of the postural fall in blood-pressure after hexamethonium was greatly increased by small venesections. Personal observations (unpublished) have shown also an increase in sensitivity to pentolinium, similar to that after chlorothiazide, after intensive treatment with mercurial diuretics; measurements of plasma-volume were not made in these cases.

On first giving chlorothiazide there is a slight shift in urinary pH towards the alkaline side, with resultant reduction in renal excretion of mecamylamine, and an increased hypotensive effect of this drug (Harington and Kincaid-Smith 1958); the same probably applies to pempidine which is excreted by the same mechanism (Harington et al. 1958). It does not apply to the quaternary ammonium compounds, such as pentolinium, in which excretion is uninfluenced by the pH of the urine.

Summary

The mode of action of chlorothiazide was studied in hypertensive patients without heart-failure, with particular regard to the potentiation of ganglion-blocking drugs.

Single intravenous doses of chlorothiazide had no appreciable effect on the blood-pressure or on the hypotensive response to a standard intravenous dose of pentolinium.

After chlorothiazide by mouth for 3 days, an increased

sensitivity to pentolinium developed in most patients. This correlated with a reduction in plasma-volume, and was abolished by replacement of the lost plasma-volume with salt-free dextran.

Postural hypotension due to chlorothiazide itself was observed in a few patients in whom the reduction in plasma-volume was large; this also was abolished after dextran infusion.

A diminution in plasma-volume is thought to be one of the main factors responsible for the increased effect of ganglion-blocking drugs in patients treated with chlorothiazide.

We are grateful to Prof. J. McMichael, F.R.S., for his encouragement and help, and to Dr. P. L. Mollison for advice on plasma-volume determinations.

REFERENCES

Beyer, K. H. (1958) *Ann. N.Y. Acad. Sci.* **71**, 363.
Bull, J. P., Ricketts, C., Squire, J. R., Maycock, W. d'A., Spooner, S. J. L., Mollison, P. L., Paterson, J. C. S. (1949) *Lancet*, i, 134.
Campbell, T. J., Frohman, B., Reeve, E. B. (1958) *J. Lab. clin. Med.* **52**, 768.
Freis, E. D., Wanko, A., Wilson, I. M., Parrish, A. E. (1958) *J. Amer. med. Ass.* **166**, 137.
— Stanton, J. R., Finnerty, F. A., Schnaper, H. W., Johnson, R. L., Rath, C. E., Wilkins, R. W. (1951) *J. clin. Invest.* **30**, 435.
Hall, R., Owen, S. G. (1959) *Lancet*, i, 403.
Harington, M., Kincaid-Smith, P. (1958) *ibid.* i, 403.
— — Milne, M. D. (1958) *ibid.* ii, 6.
Heider, C., Dennis, E., Moyer, J. H. (1958) *Ann. N.Y. Acad. Sci.* **71**, 456.
Mollison, P. L. (1956) Blood Transfusion in Clinical Medicine. Oxford.
Novello, F. S, Sprague, J. M. (1957) *J. Amer. chem. Soc.* **74**, 2028.
Restall, P. A., Smirk, F. H. (1950) *N.Z. med. J.* **49**, 206.
Smirk, F. H. (1957) High Arterial Pressure. Oxford.
Tapia, F. A., Dustan, H. P., Schneckloth, R. A., Corcoran, A. C., Page I. H. (1957) *Lancet*, ii, 831.
Wilkins, R. W., Hollander, W., Chobanian, A. W. (1958) *Ann. N.Y. Acad. Sci.* **71**, 465.
Winer, B. M. (1958) *Circulation*, **18**, 800.

HYDROCHLOROTHIAZIDE
A COMPARISON WITH CHLOROTHIAZIDE

P. R. FLEMING, M.D. Lond., M.R.C.P., SENIOR MEDICAL REGISTRAR
JOAN F. ZILVA, M.D., B.Sc., Lond., M.R.C.P., SENIOR REGISTRAR IN CHEMICAL PATHOLOGY
R. I. S. BAYLISS, M.D. Cantab., F.R.C.P.
JEANETTE PIRKIS, RESEARCH ASSISTANT
WESTMINSTER HOSPITAL, LONDON, S.W.1

THE introduction of chlorothiazide was an important advance in the treatment of œdema, because this was the first oral diuretic comparable in potency to parenterally administered mercurials (Bayliss et al. 1958a, Davis and Evans 1958, Ford et al. 1958, Laragh et al. 1958). Chlorothiazide induces diuresis chiefly by enhancing the urinary excretion of sodium and chloride (Matheson and Morgan 1958, Pitts et al. 1958). It may also promote the excretion of bicarbonate and potassium—an effect attributed to mild carbonic-anhydrase inhibition. This increased loss of potassium with liability to potassium depletion and hypokalæmia makes intermittent treatment advisable and often necessitates the concurrent administration of a potassium supplement (Bayliss 1959).

Recently hydrochlorothiazide has been introduced. This derivative of chlorothiazide differs from the parent compound in having the double bond in the heterocyclic ring saturated with two hydrogen atoms. Experimental work and early clinical experience (Ford 1959, Moyer et al. 1959) show that weight for weight hydrochlorothiazide is more potent than chlorothiazide, but this is not necessarily an advantage unless hydrochlorothiazide has some qualitative superiority in its diuretic effect. That this might be the case was suggested by the report of de Stevens et al. (1958) that in vitro hydrochlorothiazide appeared to inhibit carbonic anhydrase less than chlorothiazide, and by the claim that clinically hydrochlorothiazide induced less potassium loss (Richterich 1959, Richterich et al. 1959).

The following observations were made to determine whether there was clinically any difference in the diuretic actions of chlorothiazide and hydrochlorothiazide, to assess their relative potency, and to establish the therapeutic value of hydrochlorothiazide. The chemical and experimental methods used were those reported in an earlier study of chlorothiazide (Bayliss et al. 1958b).

Results

Diuretic Response

Changes in urinary volume and composition were followed hourly after a dose of hydrochlorothiazide in four patients fully convalescent from conditions unaccompanied by œdema. Two were given 100 mg. hydrochlorothiazide after a control period of two hours. Diuresis started in one to two hours and was associated with approximately equimolar loss of sodium and chloride ions, which reached its maximum in three to five hours (fig. 1). The pH of the urine rose and there was increased excretion of bicarbonate and potassium. These responses were qualitatively identical to those observed after chlorothiazide (Bayliss et al. 1958a).

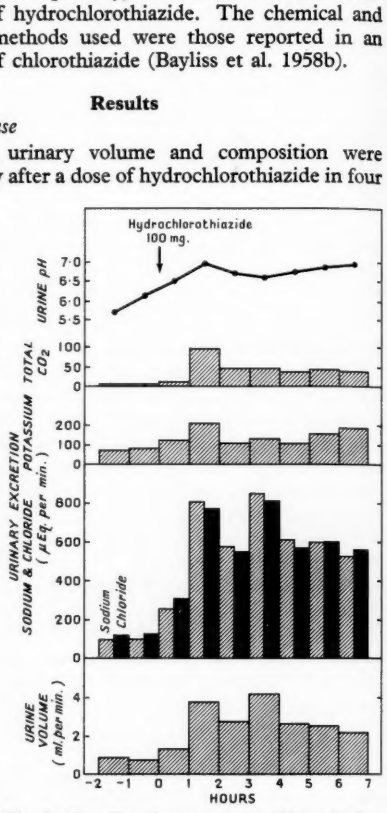


Fig. 1—The diuretic response to 100 mg. hydrochlorothiazide in a convalescent patient.

In the other two convalescent patients (I and J) the effect of 50 mg. hydrochlorothiazide was compared with that of 1 g. chlorothiazide. The results are shown in table I, and for case I in fig. 2. Both hydrochlorothiazide and chlorothiazide initiated diuresis in one to two hours,

TABLE I—URINE VOLUMES AND ELECTROLYTE EXCRETION AFTER SINGLE DOSES OF HYDROCHLOROTHIAZIDE AND CHLOROTHIAZIDE IN TWO CONVALESCENT PATIENTS

Electrolyte	Case I		Case J	
	50 mg. hydrochlorothiazide	1 g. chlorothiazide	50 mg. hydrochlorothiazide	1 g. chlorothiazide
Urine (ml./11 hr.) ..	2297	2008	5605	3523
Sodium (mEq./11 hr.) ..	209·6	181	398	246·7
Chloride (mEq./11 hr.) ..	251·2	196·6	449·6	275·3
Potassium (mEq./11 hr.)	77·2	82·9	131	115·5
Bicarbonate (mEq./7 hr.)	14·6	43·6	45·4	52·7
Na/K ratio (11 hr.) ..	2·7	2·2	3·0	2·1

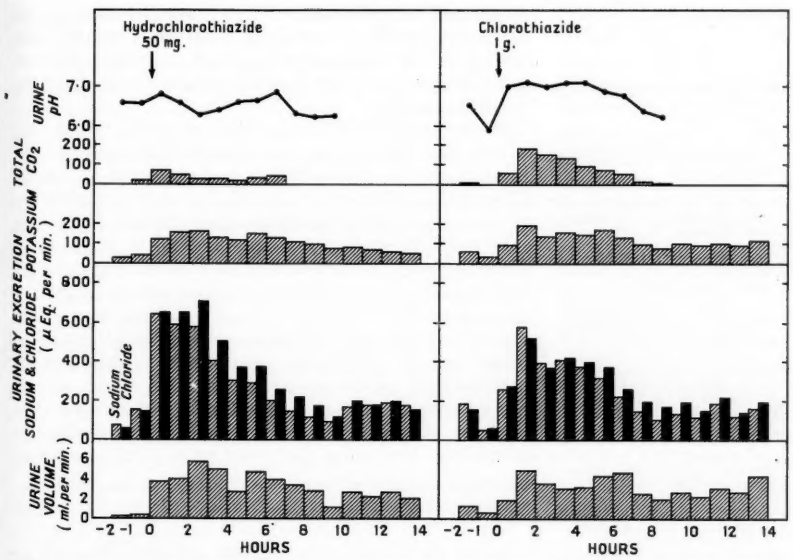


Fig. 2—A comparison of the diuretic responses to 50 mg. hydrochlorothiazide and 1 g. chlorothiazide in a convalescent patient (case I).

although in case I the diuresis started sooner after hydrochlorothiazide. The effect had largely waned after eleven hours. During this time more chloride than sodium ions were excreted, particularly after hydrochlorothiazide. Both drugs increased the excretion of bicarbonate, the amounts excreted being almost equal in case J but chlorothiazide producing a greater loss than hydrochlorothiazide in case I. Both drugs increased the excretion of potassium, the losses being almost equal in case I but greater after hydrochlorothiazide in case J. The amount of sodium excreted in proportion to the amount of potassium excreted (Na/K ratio) was greater after hydrochlorothiazide than after chlorothiazide.

The two drugs were also compared in six healthy ambulant subjects, each of whom received at intervals 25 and 50 mg. hydrochlorothiazide and 0·5 g. chlorothiazide. Urine volumes and electrolyte excretion were studied for twelve hours after the diuretic was given. The individual results are shown in fig. 3, and the mean results for the group in table II. The diuretic responses showed some quantitative differences (see below), but there was no statistical difference in the amount of potassium excreted after chlorothiazide and after either dose level of hydrochlorothiazide. After 25 mg. hydrochlorothiazide, however, the amount of sodium excreted in relation to the loss of potassium (Na/K ratio) was greater ($0·01 < P < 0·02$) than after 0·5 g. chlorothiazide. On the other hand, because of individual variation in response, the Na/K ratio after 50 mg. hydrochlorothiazide was not statistically different ($0·1 < P < 0·2$) from that after 0·5 g. chlorothiazide. For example, in subjects A and C (fig 3) more sodium per unit of potassium excreted was eliminated after 50 mg. hydrochlorothiazide than after 0·5 g. chlorothiazide, but in subject F there was a large potassium loss and the Na/K ratio was low.

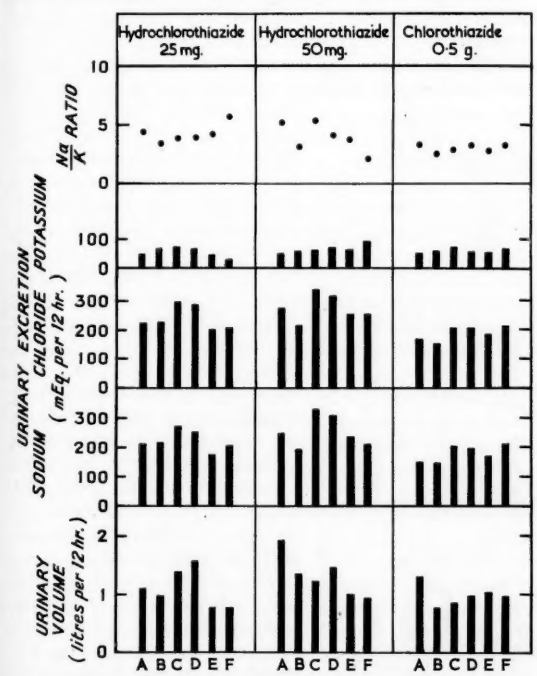

Hydrochlorothiazide 25 mg.
Hydrochlorothiazide 50 mg.
Chlorothiazide 0·5 g.
Na/K RATIO
URINARY EXCRETION SODIUM CHLORIDE POTASSIUM (mEq. per 12 hr.)
URINARY VOLUME (litres per 12 hr.)
A B C D E F
CASE

Fig. 3—The diuretic responses in 6 healthy subjects after 25 and 50 mg. hydrochlorothiazide and 0·5 g. chlorothiazide.

TABLE II—MEAN URINE VOLUME AND ELECTROLYTE EXCRETION IN SIX HEALTHY SUBJECTS FOR TWELVE HOURS AFTER 25 AND 50 MG. HYDROCHLOROTHIAZIDE AND 0·5 G. CHLOROTHIAZIDE

—	Hydrochlorothiazide		Chlorothiazide 0·5 g.
	25 mg.	50 mg.	
Volume (ml.)	1088 ± 322*	1304 ± 354	973 ± 184
Sodium (mEq.) ..	222 ± 34·7	250 ± 54·2	180 ± 26·7
Chloride (mEq.) ..	239 ± 41·7	274 ± 47	185 ± 25·1
Potassium (mEq.) ..	53 ± 14·9	66 ± 15·7	59 ± 7·7
Na/K ratio	4·3 ± 0·95	4·0 ± 1·2	3·1 ± 0·36

* Standard deviation.

Comparative Potency

In the two convalescent patients I and J, 50 mg. hydrochlorothiazide promoted a greater diuresis and a greater loss of sodium and chloride than 1·0 g. chlorothiazide (table I). In the six healthy subjects, 25 mg. hydrochlorothiazide did not induce a significantly greater urine volume ($0·2 < P < 0·5$) than 0·5 g. chlorothiazide, although the loss of sodium and chloride was slightly greater ($0·02 < P < 0·05$ for both ions). The urine volume after 50 mg. hydrochlorothiazide was also not significantly larger ($0·05 < P < 0·1$) than after 0·5 g. chlorothiazide, but the excretion of sodium was greater ($0·01 < P < 0·02$) and also the output of chloride ($0·001 < P < 0·01$). Judging by the amount of sodium excreted, 50 mg. hydrochlorothiazide was definitely more potent, and 25 mg. hydrochlorothiazide

TABLE III—SUMMARY OF CLINICAL RESULTS

Case no.	Sex	Age (yr.)	Diagnosis	Comment
1	F	69	Hypertensive and ischæmic heart-disease	100 mg. hydrochlorothiazide b.d. Good response. 6 lb. weight loss in 7 days
2	F	35	Cor pulmonale	100 mg. hydrochlorothiazide b.d. Good response. 27 lb. weight loss in 14 days
3	M	74	Hypertensive heart-disease	50 mg. hydrochlorothiazide b.d. Good response. 16 lb. weight loss in 6 days
4	M	49	Aortic incompetence	Unresponsive to chlorothiazide, mersalyl, and 50 mg. hydrochlorothiazide b.d.
5	F	30	Mitral stenosis	Unresponsive to chlorothiazide, mersalyl, and 50 mg. hydrochlorothiazide b.d.
6	M	47	Hypertensive heart-disease	Unresponsive to chlorothiazide. 8 lb. weight loss in 48 hr. after two doses of 100 mg. hydrochlorothiazide. Died in uræmia
7	F	66	Mitral stenosis	Equal response to 1 g. chlorothiazide and 200 mg. hydrochlorothiazide
8	M	54	Cirrhosis	100 mg. hydrochlorothiazide more potent than 1 g. chlorothiazide (see table IV)
9	M	45	Cirrhosis	200 mg. hydrochlorothiazide more potent than 2 g. chlorothiazide (see fig. 4)
10	M	53	Mitral incompetence	0·5 g. chlorothiazide more potent than 50 mg. hydrochlorothiazide

equal to, or slightly more potent than, 0·5 g. chlorothiazide in these healthy subjects.

Clinical Observations

The effect of hydrochlorothiazide was studied in ten œdematous patients (table III). In the first three, suffering from congestive cardiac failure, it was the only diuretic used. The dose was 50 or 100 mg. twice daily, and a supplement of 1 g. potassium chloride was given twice daily on alternate days. These patients responded with a satisfactory diuresis, and no significant abnormalities in the serum levels of sodium, potassium, or chloride developed. The first patient lost 6 lb. in weight in seven days; the second 27 lb. in fourteen days; and the third 16 lb. in six days.

In two patients with long-standing cardiac failure due to valvular disease (cases 4 and 5), who had become unresponsive to chlorothiazide and to mersalyl, hydrochlorothiazide 100 mg. daily failed to induce significant diuresis. Both these patients had mild azotæmia and were excreting very small amounts of sodium in their urine. However, even in the presence of a reduced glomerular filtration-rate, hydrochlorothiazide may induce diuresis—to the patient's detriment. Case 6 presented with severe paroxysmal nocturnal dyspnœa and congestive cardiac failure due to hypertensive heart-disease. No diuresis occurred after 1 g. chlorothiazide twice daily, and, despite a blood-urea of 342 mg. per 100 ml., it was considered justifiable to give hydrochlorothiazide in an attempt to relieve the distressing and potentially lethal attacks of cardiac asthma. Two doses of 100 mg. hydrochlorothiazide produced pronounced diuresis leading to a loss of 8 lb. in weight in forty-eight hours, but the blood-urea level rose to 420 mg. per 100 ml. and the patient died in uræmia the next day.

TABLE IV—DIURETIC RESPONSE TO VARIOUS DOSES OF CHLOROTHIAZIDE AND HYDROCHLOROTHIAZIDE IN A PATIENT WITH HEPATIC CIRRHOSIS

—	Urine volume (ml./24 hr.)	mEq./24 hr.			Body-weight (lb.)
		Na	K	Cl	
0·25 g. chlorothiazide ..	1740	197	42	181	113
1·0 g. ,,	1620	200	76	188	115
25 mg. hydrochlorothiazide	1540	183	86	215	113
50 mg. ,,	1610	185	90	226	114
100 mg. ,,	1800	236	76	260	115

Chlorothiazide and hydrochlorothiazide were compared in the remaining four patients. In one (case 7) the responses to 1 g. chlorothiazide and 200 mg. hydrochlorothiazide daily were the same in respect of urine volume and the excretion of sodium, potassium, and chloride. In case 8, who had ascites due to hepatic cirrhosis, and whose weight remained constant during the period of observation, a comparison was made between single doses of 0·25 and 1·0 g. chlorothiazide and of 25, 50, and 100 mg. hydrochlorothiazide. On each occasion the volume of urine and the amount of sodium excreted differed little, except that 100 mg. hydrochlorothiazide induced a slightly greater loss of sodium and chloride (table IV). Subsequently this patient has been maintained equally well on either 0·5 g. chlorothiazide or 50 mg. hydrochlorothiazide given on alternate days.

The results in case 9, who had cirrhosis of the liver with gross ascites and œdema, are shown in fig. 4. During the initial control period (days 1–5) he gained weight and excreted very small amounts of sodium,

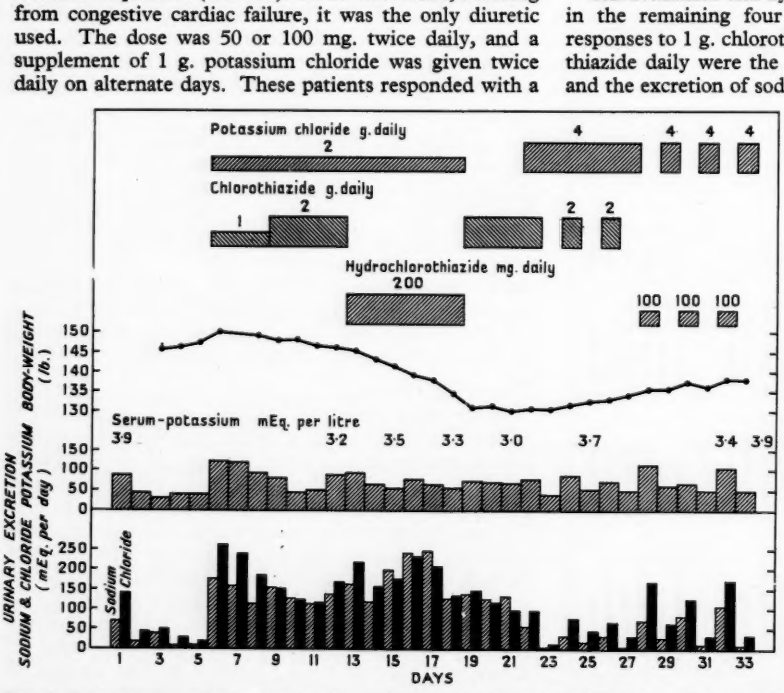


Fig. 4—A comparison of the effect of chlorothiazide and hydrochlorothiazide in a patient with hepatic cirrhosis (case 9).

which were often less than the urinary loss of potassium. Chlorothiazide on days 6–12 induced good diuresis which was, however, not maintained although the dose was increased. Potassium excretion was enhanced and the serum level fell from 3·9 to 3·2 mEq. per litre, despite a daily supplement of 2 g. potassium chloride. Hydrochlorothiazide in a dose of 100 mg. twice daily on days 13–18 induced a further good diuresis and a more rapid fall in weight. The loss of sodium was strikingly enhanced and there was no further fall in the serum-potassium level. A return to 1 g. chlorothiazide twice daily on days 19–22 resulted in a smaller diuresis and no further loss of weight. On days 24–32 the effect of 2 g. chlorothiazide on alternate days was compared with 100 mg. hydrochlorothiazide on alternate days. Neither drug prevented reaccumulation of œdema fluid and a gain in weight. Both enhanced the excretion of more chloride than sodium ions, with a consequent greater loss of potassium, and this effect was particularly striking after hydrochlorothiazide on days 28 and 32.

In case 10, with mitral incompetence, the effect of single doses of 0·5 g. chlorothiazide on four occasions was compared with that after 50 mg. hydrochlorothiazide on six occasions. During the three-week period of observation, the patient failed to lose his œdema and gained 11 lb. in weight. The diuretic responses were irregular, but chlorothiazide promoted the greatest daily loss of sodium (287 mEq.) whereas the largest amount of sodium excreted after hydrochlorothiazide was 235 mEq.

Discussion

Hydrochlorothiazide is clearly more potent weight for weight than chlorothiazide. In convalescent patients 50 mg. induced a greater loss of sodium and water than 1 g. chlorothiazide; and in healthy young subjects 25 mg. promoted greater sodium excretion than 0·5 g. chlorothiazide, although the amount of urine passed was not significantly larger. In both groups, therefore, hydrochlorothiazide was 20 times more potent than chlorothiazide. In patients with œdema, however, this relationship may not apply. In case 7, for example, 200 mg. hydrochlorothiazide was equivalent to 1 g. chlorothiazide (a ratio of 1 to 5), whereas in case 8, 0·25 and 1 g. chlorothiazide and 25 and 50 mg. hydrochlorothiazide all produced very similar responses, only being exceeded by the effect of 100 mg. hydrochlorothiazide. In case 9 hydrochlorothiazide was more potent than chlorothiazide in a tenth the dose, and in case 10 the relative potency was also 1 to 10. Thus it seems that in the treatment of œdematous patients hydrochlorothiazide will be effective in an amount one-tenth that of chlorothiazide, and that except in exceptional circumstances the daily dose will be 50–150 mg. In some instances hydrochlorothiazide may induce diuresis when mersalyl or chlorothiazide have failed. The greater potency of hydrochlorothiazide may be related to better intestinal absorption; to the fact that, unlike chlorothiazide, hydrochlorothiazide is not excreted in the bile and hence more is available for renal elimination; or to greater secretion of the drug by the renal tubules where it exerts its effect. The renal clearance of both diuretics is more than the glomerular filtration-rate, and the clearance of hydrochlorothiazide greater than that of chlorothiazide (K. Beyer, personal communication).

With regard to qualitative differences in the diuretic response induced by the two drugs, the data in table I indicate that hydrochlorothiazide does not promote the excretion of bicarbonate to the same degree as does chlorothiazide, and this is reflected in a smaller change of urinary pH than after chlorothiazide (fig. 2). There is, however, little difference between the two drugs in the promotion of potassium excretion. In the convalescent and healthy subjects potassium excretion was increased by hydrochlorothiazide, and in the latter group there was no statistical difference in the amount of potassium lost after the two drugs. In œdematous patients hydrochlorothiazide also increases potassium loss, particularly when sodium retention is severe and more chloride than sodium is excreted (fig. 4). Although after hydrochlorothiazide there may be less potassium excreted per unit of sodium eliminated than after chlorothiazide, potassium loss may nonetheless be considerable; and the same precautions as with chlorothiazide must be taken to prevent potassium depletion. Hydrochlorothiazide should whenever possible be given intermittently to œdematous patients, and if treatment has to be continued for more than a few days supplements of potassium chloride must be given.

Summary

Hydrochlorothiazide is an effective diuretic. In healthy subjects it is, weight for weight, some 20 times more potent than chlorothiazide. In œdematous patients there are considerable individual variations, but usually hydrochlorothiazide is some 10 times more potent than the parent compound.

Hydrochlorothiazide promotes less bicarbonate excretion than chlorothiazide, but the loss of potassium after the two drugs is not significantly different. For this reason hydrochlorothiazide should be given intermittently and when treatment is continued for more than a few days supplements of potassium chloride are necessary.

Our thanks are due to colleagues for allowing us to study patients under their care; and to Messrs. Merck Sharp & Dohme for supplies of hydrochlorothiazide (' Hydrosaluric ').

REFERENCES

Bayliss, R. I. S. (1959) *Brit. med. J.* i, 41.
— Marrack, D., Pirkis, J., Rees, J. R., Zilva, J. F. (1958a) *Ann. N.Y. Acad. Sci.* **71**, 442.
— — Zilva, J. F. (1958b) *Lancet*, i, 120.
Davis, D. W., Evans, B. (1958) *Brit. med. J.* i, 967.
de Stevens, G., Werner, L. H., Halamandaris, A., Ricca, S. (1958) *Experientia*, **14**, 463.
Ford, R. V. (1959) *Sth med. J.* **52**, 40.
— Rochelle, J. B., Handley, C. A., Moyer, J. H., Spurr, C. L. (1958) *J. Amer. med. Ass.* **166**, 129.
Laragh, J. H., Heinemann, H. O., Demartini, F. E. (1958) *ibid.* p. 145.
Matheson, N. A., Morgan, T. N. (1958) *Lancet*, i, 1195.
Moyer, J. H., Fuchs, M., Irie, S., Bodi, T. (1959) *Amer. J. Cardiol.* **3**, 113.
Pitts, R. F., Kruck, F., Lozano, R., Taylor, D. W., Heidenreich, P. A., Kessler, R. H. (1958) *J. Pharmacol. exp. Therapeut.* **123**, 89.
Richterich, R. (1959) *Klin. Wschr.* **7**, 355.
— Spring, P., Thönen, H. (1959) *Schweiz. med. Wschr.* **89**, 353.

DIHYDROCHLOROTHIAZIDE IN CONTROL OF ASCITES

D. N. S. KERR
M.B. Edin., M.S. Wisconsin, M.R.C.P., M.R.C.P.E.
MEDICAL REGISTRAR

A. E. READ
M.D. Lond., M.R.C.P.
MEDICAL REGISTRAR AND TUTOR

SHEILA SHERLOCK
M.D. Edin., F.R.C.P., F.R.C.P.E.
PHYSICIAN AND LECTURER

DEPARTMENT OF MEDICINE,
POSTGRADUATE MEDICAL SCHOOL OF LONDON, W.12

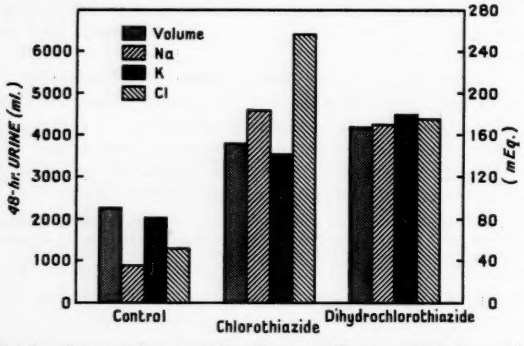
SOON after its introduction into clinical practice in 1957 (Moyer et al. 1957), chlorothiazide was accepted as the most effective oral diuretic available. In comparison with the injected mercurial diuretics its only disadvantages were higher cost and a tendency to increase urinary potassium excretion. The loss of potassium can usually be compensated by means of oral supplements, but in patients with liver disease, in whom secondary aldosteronism is severe, the largest tolerated oral doses of

TABLE I—EFFECTS OF CHLOROTHIAZIDE AND DIHYDROCHLOROTHIAZIDE ON URINE VOLUME AND ELECTROLYTES

Day	Volume (ml. per 24 hr.)						Sodium (mEq. per 24 hr.)						Potassium (mEq. per 24 hr.)						Chloride (mEq. per 24 hr.)			
	Case no.					Mean	Case no.					Mean	Case no.					Mean	Case no.			Mean
	1	2	3	4	5		1	2	3	4	5		1	2	3	4	5		1	2	3	
Control 1	1300	1860	1040	640	200	1010	9	33	4	26	3	15	30	73	41	36	10	38	16	76	8	33
„ 2	1400	2000	1640	930	300	1250	2	26	6	32	8	15	28	54	56	53	22	43	16	36	20	21
Chlorothiazide 1	1960	3600	2400	1400	300	1930	30	234	93	94	21	94	130	83	86	78	25	80	42	302	94	146
„ 2	1890	2800	2150	1600	600	1810	27	196	106	90	30	92	66	96	67	64	46	68	13	212	114	113
Dihydrochlorothiazide 1	1700	2700	1450	2390	770	1800	14	97	19	164	58	70	72	122	77	133	54	92	30	194	45	90
„ 2	1900	2700	3750	2500	730	2320	11	143	116	184	43	100	63	111	135	105	40	91	34	162	68	88

potassium may be insufficient to prevent hypokalæmia (Read et al. 1958). This is a serious problem as these patients are liable to pass into hepatic coma as the serum-potassium falls.

The recently prepared dihydro-derivative of chlorothiazide ('Esidrex', 'Hydrosaluric') gives promise of being many times more potent, weight-for-weight, than the parent compound and has been said to cause less potassium excretion than chlorothiazide (Ford 1959, Richterich 1959, Richterich et al. 1959). We have therefore carried out a small pilot trial to compare dihydrochlorothiazide and chlorothiazide in the control of ascites in patients with liver disease.



Total urinary volume, and urinary sodium, potassium, and chloride over 48 hours, during control and two treatment periods. (Volume, sodium, and potassium: mean of 5 cases; chloride: mean of 3 cases.)

Method

Five patients with ascites and œdema due to liver disease (four with cirrhosis, one with primary hepatoma) were kept in bed (although allowed up to toilet) and given a diet containing 22 mEq. sodium daily. Fluid intake was adjusted by the patients themselves. After a period of at least a week, the patients were given a course of 500 mg. chlorothiazide 6-hourly or dihydrochlorothiazide 50 mg. 6-hourly, for four doses in each case. Two patients were given chlorothiazide first, and three dihydrochlorothiazide first. In each patient the second drug was given at least 5 days after the other.

Urine volume and electrolytes were measured over a 2-day control period and for 2 days after the administration of each drug. Serum-electrolytes were measured the day before and the day after administration of the drugs. In two patients serum-electrolytes were also measured for several days after the drug, but the maximum alteration occurred on the day following administration.

Results

During the control period all patients excreted more than 4 mEq. of sodium per day. Such patients with fluid retention usually respond to diuretics (Read et al. 1958), and in fact all five patients had significant diuresis with both the drugs.

The increase in urinary volume and urinary sodium, potassium, and chloride excretion were similar after the two drugs, the differences being nonsignificant (table I and figure). The only consistent changes in serum-electrolytes were a fall in serum potassium and chloride (table II). There was a slight rise in serum-bicarbonate in each case after dihydrochlorothiazide, but no consistent change after chlorothiazide. A careful watch was kept for premonitory symptoms of hepatic precoma. After either drug, one patient (who had a previous history of several episodes of coma) developed typical clinical features of precoma, and electroencephalography showed gross slow activity. The symptoms were more pronounced after dihydrochlorothiazide, which was given second, but this may have been because of greater potassium loss (233 mEq. compared with 179, in the 2-day collection periods) or because the initial serum-potassium level was lower on the second occasion.

Discussion

The similarity in response after the two drugs suggests that 500 mg. of chlorothiazide and 50 mg. of dihydrochlorothiazide are equivalent doses. As the dose-response curves of these drugs are not linear it does not follow that dihydrochlorothiazide is always ten times more powerful than chlorothiazide. Other estimates are that it is twenty times as powerful on a weight-for-weight basis (Sele 1958, Kennedy and Crawford 1959, Richterich 1959). This of course is of no value to the patient, who simply swallows a slightly smaller pill, but the cost of production of smaller quantities of the newer drug may be lower than that of equivalent doses of chlorothiazide.

The finding that this new drug has no less tendency to cause potassium depletion than its predecessor is disappointing; it implies that dihydrochlorothiazide must be used with the same care as chlorothiazide in patients with liver disease, particularly those with a previous history of

TABLE II—CHANGES IN SERUM-ELECTROLYTES FOLLOWING CHLOROTHIAZIDE AND DIHYDROCHLOROTHIAZIDE

—	Sodium (mEq. per l.)						Potassium (mEq. per l.)						Chloride (mEq. per l.)						Bicarbonate (mEq. per l.)					
	Case no.					Mean	Case no.					Mean	Case no.					Mean	Case no.					Mean
	1	2	3	4	5		1	2	3	4	5		1	2	3	4	5		1	2	3	4	5	
Following chlorothiazide	+3	+2	−8	+5	−3	−0·2	−0·7	0	−0·3	−1·2	+0·1	−0·4	−1	−3	−10	−2	−2	−3·6	−10	+1	+3	−3	+1	−1·6
Following dihydrochlorothiazide	+2	+1	−3	0	−8	−1·6	−0·7	−0·2	−1·4	−1·3	+0·4	−0·6	−4	−4	−5	−2	+2	−2·6	+4	+3	+3	+3	0	+2·6

hepatic precoma. Potassium supplements should be given routinely and regular measurements of serum-electrolytes carried out.

Summary

Five patients with liver disease were treated with alternate courses of chlorothiazide and dihydrochlorothiazide. A similar diuresis was produced by the two drugs, and potassium excretion was increased by roughly equal amounts.

The diuretic effect of 50 mg. of dihydrochlorothiazide is equivalent to that of 500 mg. of chlorothiazide.

Both of these drugs are effective diuretics in liver disease, but both are liable to cause hypokalæmia and should therefore be given cautiously and with adequate potassium supplements.

We are grateful to Dr. Thomas Hanley, of Ciba Laboratories Ltd., for supplies of dihydrochlorothiazide; to Dr. R. M. Haslam and Miss J. R. McLaren for biochemical assistance; to Miss R. Harrison and her staff for preparation of the diets; and to Sister E. Jones and Sister M. Shipton for care of the patients and meticulous collection of the specimens. The Medical Research Council kindly gave financial assistance.

REFERENCES

Ford, R. V. (1959) *Sth. med. J., Nashville*, **52**, 40.
Kennedy, G. C., Crawford, J. D. (1959) *Lancet*, **i**, 866.
Moyer, J. H., Ford, R. V., Spurr, C. L. (1957) *Proc. Soc. exp. Biol., N.Y.* **95**, 529.
Read, A. E., Haslam, R. M., Laidlaw, J., Sherlock, S. (1958) *Brit. med. J.* **i**, 963.
Richterich, R. (1959) *Klin. Wschr.* **7**, 355.
— Spring, P., Thonen, H. (1959) *Schweiz. med. Wschr.* **89**, 353.
Sele, V. (1958) *Ugeskr. Læg.* **120**, 1592.

A CONVULSIVE SYNDROME IN NEWBORN FOALS RESEMBLING PULMONARY SYNDROME IN THE NEWBORN INFANT

LEO W. MAHAFFEY
B.V.Sc. Sydney, M.R.C.V.S.
OF THE EQUINE RESEARCH STATION, THE ANIMAL HEALTH TRUST, NEWMARKET

P. D. ROSSDALE
B.A. Cantab., M.R.C.V.S.
OF ROMNEY HOUSE, NEWMARKET

THE term "pulmonary syndrome" was coined by Bound et al. (1956) for a condition fatal during the first week of life—in which the lungs show "resorption atelectasis" and one or more of the following: (1) hyaline membrane, (2) intra-alveolar hæmorrhage, (3) pulmonary œdema. "Pulmonary hyaline-membrane syndrome" itself has long been recognised and has "provoked a deluge of anatomic, pathologic and experimental reports and studies" (Laufe and Stevenson 1956). Nevertheless its ætiology and pathogenesis remain obscure.

In 1957 we described an acute convulsive syndrome in newborn thoroughbred foals (Mahaffey and Rossdale 1957a and b). From discussions with Dr. R. E. Bonham Carter and his colleagues at University College Hospital, and examination of lung sections (provided by Dr. A. M. Barrett of the department of pathology at Cambridge), we conclude that convulsive syndrome in foals and the pulmonary syndrome in infants are closely similar.

Clinical Features

In the Newmarket area about 1% of thoroughbred foals develop a convulsive syndrome soon after birth, the onset being occasionally delayed as long as 12 hours. The condition always follows a very easy delivery after which the foal appears normal at first. A little later, often while standing, or while trying to get to its feet for the first time it may be observed jerking its head up and down. After this it becomes unsteady on its feet and then suddenly falls down. It may emit a barking noise for a short time, and the clonic movements are followed by violent convulsions.

There are galloping movements and powerful contractions of the neck and back, often accompanied by profuse sweating. The pulse and respiration rates are greatly increased.

So great and persistent are the early convulsive movements that the combined efforts of four men may be required to restrain the animal. When the symptoms subside or are brought under control by anticonvulsant drugs, the foal lapses into semicoma, but convulsive movements are readily provoked again by various stimuli. This stage may last for some days and meanwhile the foal requires constant attention and feeding by stomach-tube. About half of carefully nursed cases recover completely, without any residual effects, but they pass through a temporary phase of apparent blindness and aimless wandering before they learn to suck from their mother.

The pulmonary syndrome of infants is commonly associated with prematurity and cæsarean section. In mares this operation is very rarely practised, but as judged by the length of gestation, convulsive foals are not premature. In most other respects, however, the two syndromes are remarkably alike.

Generally both infant and foal appear normal for a short time and the first respiratory movements occur without any noticeable difficulty, but the onset of symptoms is usually quite rapid, with early respiratory distress. Both make a respiratory noise (and grunting in infants may have a similar origin to barking in foals) though the keel-like shape of the chest in foals makes it difficult for sternal recession to be a feature. We have not detected cyanosis in foals, but there is often marked pallor in their mucous membranes. In one series of cases of pulmonary syndrome 34% developed convulsions and 10% had signs of cerebral irritation (Bound et al. 1956). Of the cases where cerebral irritation had been diagnosed clinically and a necropsy done 63% were found to have no cerebral lesion, but pathological changes in the lungs alone. The symptoms of restlessness, irritability, and shrill high-pitched cry described by Bound are reminiscent of the sick foal. In both, there may be initial "jerkiness" before the development of convulsions and after their subsidence these can easily be provoked anew by external stimuli.

Neither condition is associated with infective agents. We have never found evidence of cranial damage in foals at autopsy. In contrast to the infant at birth the bones of the foal's skull are quite dense and the sutures are occupied by thick unyielding cartilage.

Pathology

Macroscopic Appearances

Spector described the lungs of infants dying of pulmonary syndrome (Bound et al. 1956) as voluminous, dark purple in colour, with a dark and solid cut surface resembling fœtal liver; these findings might have been applied to foals which have died following convulsive syndrome. Furthermore, we have never discovered any other significant macroscopic lesions. From examination of the lungs of a considerable number of newborn foals, we are certain that complete expansion is very rapid. Even in one foal which was allowed to live for only ten minutes after delivery there was apparently uniform expansion of both lungs, which were feathery in texture and the palest pink throughout. Portions from all parts of these floated in fixative. By contrast the lungs of six out of seven convulsive foals showed almost no aerated areas

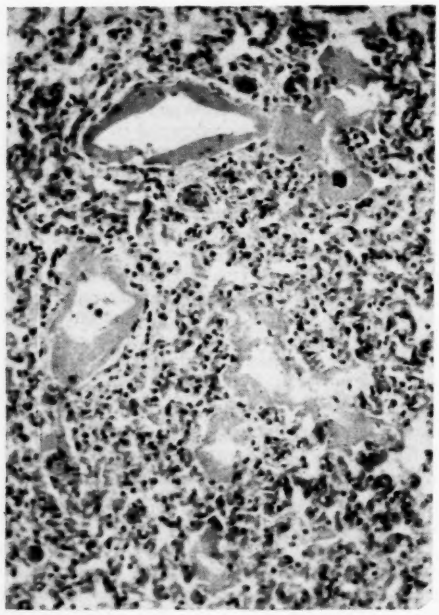


Fig. 1—Hyaline structures in the lung of a newborn foal which had died from convulsive syndrome (×100).

and pieces from most parts sank rapidly in fixative, while the seventh showed very patchy aeration. In all seven animals the ductus arteriosus was more patent than in any normal foal of corresponding age which we have ever examined.

Histology

Microscopically the outstanding and consistent lesion was the extensive resorption atelectasis.

In this the normal alveolar patterns have almost completely disappeared and patency appears to end at the alveolar ducts. It is as though the alveoli have collapsed completely and their capillaries lie side by side; although these do not appear individually to contain more blood than normal, the result is a general appearance of widespread congestion. Because of the collapse the interlobular septa are much wider and more obvious than normal, and their blood-vessels are very prominent and congested. "Initial" epithelium persists much longer than normal and can be found even at four days.

Since our first observations (Mahaffey and Rossdale 1957b) we have discovered in one of our earliest cases hyaline structures as characteristic and prominent as any we have been shown in sections from infants (fig. 1). In another case there was more than a suggestion of this material. Thus all the classical pathological features of "hyaline membrane" disease are to be found in at least some of the foals with convulsive syndrome.

The only other lesion we have found is in the spleen.

In convulsive foals which survive for more than a day the malpighian nodes become markedly depleted of cells, and, in two cases which died at 4 days, they appeared as structureless hyaline masses. This is not a specific change; we have seen it in foals dying of hæmolytic disease of the newborn or neonatal pneumonia—cases in which we presume there was some degree of anoxia.

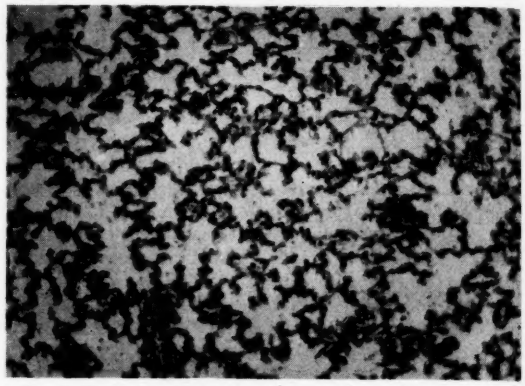


Fig. 2—Typical fœtal lung (embryo 1 from rabbit A) (×32).
Note the regularity of the alveoli in size and shape, and the lining of "initial" epithelium.

We have not found any lesions in the brain and this is consistent with the completeness of the recovery in favourable cases. The latter never show any residual disability and we know of at least two which have won good races.

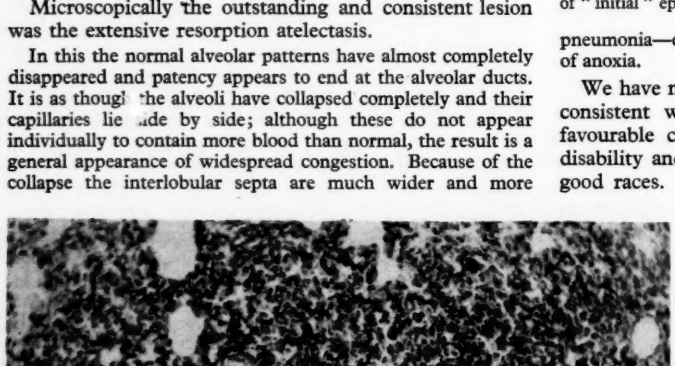


Fig. 3—Lung from embryo III of rabbit A: in this a total of 0·75 ml. blood had been removed before respiration began (×34).
Note widespread collapse of alveoli and the apparent termination of patency at the alveolar ducts. This appearance is strikingly similar to the lungs of a foal following convulsive syndrome, although no hyaline structures are present.

Conditions Under which Foal Disease Occurs

The convulsive syndrome appears to be seen only in foals born indoors, under human supervision. This is the general practice in the thoroughbred breeding centres of England, Ireland, France, and Italy, and the syndrome occurs in all these countries. By contrast the condition is apparently unknown in Australia where thoroughbred mares generally give birth to their young, unattended, in open paddocks. Further, even in England, the syndrome has not been noted in breeds which have their foals out of doors and away from human assistance. Thus it seems likely that the cause is in some way related to the conduct of parturition.

Parturition under natural conditions differs in various ways from parturition conducted indoors by man.

Variable degrees of traction are usually practised by attendants when the head

RESULTS OF ANIMAL EXPERIMENTS

Animal	Procedure	Findings at necropsy	
		Macroscopic	Histological
Rabbit A: 4 embryos			
I	Killed immediately	..	Typical fœtal lung: alveoli regular in size and shape, and lined with " initial " epithelium (fig. 2)
II	Placed in incubator at birth: placenta detached at 30 min.: killed at 90 min. by bilateral pneumothorax	..	Relative collapse, but good alveolar pattern throughout
III	0·25 ml. blood removed from umbilical vein (no more possible): 0·5 ml. blood removed from the heart: placed in incubator for 90 min. then killed	Both lungs visibly collapsed. No visible damage to heart	Widespread collapse of alveoli (different from that seen in pneumothorax): patency appeared to end at alveolar ducts (fig. 3). *Striking similarity to lungs of foal following convulsive syndrome—no definite hyaline membrane*
IV (control)	Delivered spontaneously per vaginam: survival for 90 min., then killed	..	Well expanded alveoli throughout, similar to normal neonatal lung
Rabbit B: 6 embryos			
I (control)	Removed with placenta attached: cord broken at 5 min.: breathed well: killed after 2 hours	Lungs well expanded: normal colour	Normally expanded aerated lung
II, III, IV, V	Cord cut before respiration started: breathed well for 90 min.: killed	II, III—normal expansion IV, V—obvious areas of collapse or suboptimal expansion	" No hyaline membrane, and little atelectasis of resorption type, but alveoli in macroscopically abnormal areas were smaller than in control
VI	Cord clamped before respiration started: breathed well for 90 min.: killed	Appearances similar to those in IV and V	"
Bitch: 3 embryos			
I (control)	Removed with placenta attached: cord broken at 5 min.: breathed well: killed after 2 hours	Lungs well expanded: normal colour	Normally expanded aerated lung
II	7 ml. of blood removed from umbilical vein before onset of respiration and rupture of amnion: cord clamped and severed: normal respiration: killed after 2 hours	Substantial areas of lung with suboptimal expansion or collapse	Mixture of suboptimal expansion and contiguous collapse
III	Treatment as embryo II, but 10 ml. of blood removed	Very little normal expansion	Changes more widespread than in embryo II

and forelegs are emerging from the vulva. The amnion is prematurely ruptured by hand, the legs are grasped and a pull is exerted upon them.

Very frequently the foal is given an enema, sometimes a castor oil mixture is administered by mouth, and there often is a tendency to hurry a foal to suck its mother. More important, we think, is the fact that the umbilical cord is ruptured with such haste that the newborn foal (weighing 100–120 lb.) is deprived of an average of 1020 ml. of blood and often 1500 ml.—probably about 30% of its potential blood-volume (Rossdale and Mahaffey 1958). Under normal conditions a mare usually rests for a period of up to half an hour after parturition, during which the foal also is inactive. The cord remains intact and is not broken until the mare (sometimes the foal) attempts to get to its feet. Meanwhile virtually all the blood in the placenta has passed back into the circulation of the foal, and it is difficult to collect even 50 ml. of blood when the cord ruptures at this stage.

The Investigations

To decide whether premature severance of the cord is the cause of the syndrome we are comparing the incidence of convulsion in foals treated differently in this respect. The results of this will be published later.

Meanwhile we have made some preliminary experiments in rabbits and in puppies to see whether changes in the lungs are demonstrable in those which are deprived of placental blood, or in those which have their blood-volume lessened at or before the onset of respiration.

Four rabbits were subjected to cæsarean section 24 hours before the termination of gestation (estimated from the date when mating last occurred). Two rabbits (including A) were anæsthetised with pentobarbitone and two rabbits (including B) were anæsthetised with ether. Ether was much more satisfactory because it had no observable depressant effects upon the fœtus. An attempt was made in each case to return one fœtus as a control, and the others were subjected to some form of interference, calculated to disturb their blood-volume (whenever possible), before the amnion was broken and before the first gasp was observed. A similar procedure was followed with a bitch, in which ether anæsthesia was also used.

The findings are summarised in the table and show that in rabbit and dog embryos macroscopical and histological appearances resembling those found in the lungs of foals dying of convulsive syndrome have been produced. Whether these effects are specific and directly related to circulatory disturbance at the time of initial lung expansion (possibly supporting Jäykkä's [1957] work on capillary erection and lung expansion), or are non-specific, requires further investigation.

Summary

In an acute convulsive syndrome seen in newborn thoroughbred foals the clinical findings are closely similar to those in the "pulmonary syndrome" in newborn infants. In both conditions the lungs show extensive resorptive atelectasis with almost complete disappearance of the alveloar pattern and persistence of " initial " epithelium.

This syndrome seems to affect only thoroughbred foals delivered with human intervention. According to current practice the cord is tied immediately which deprives the foal of 30% of its blood-volume.

To ascertain whether such reduction in blood-volume affected expansion of the lung, experiments using four rabbits and a bitch were undertaken. Histologically the lungs of these animals showed appearances strikingly similar to the lungs of a foal following convulsive syndrome.

We should like to thank Dr. R. E. Bonham Carter of University College Hospital and Dr. T. K. Ryan of Addenbrooke's Hospital, Cambridge, for their encouragement and helpful discussion.

Mr. W. B. Singleton, M.R.C.V.S., was good enough to perform the cæsarean operation on the bitch.

REFERENCES

Bound, J. P., Butler, N. R., Spector, W. (1956) *Brit. med. J.* ii, 1191.
Jäykkä, S. (1957) *Acta pædiat., Stockh.* **46**, suppl. 112.
Laufe, L., Stevenson, S. (1956) *Obstet. Gynec.* **8**, 451.
Mahaffey, L. W., Rossdale, P. D. (1957a) *Vet. Rec.* **69** (part 2), 1277.
— — (1957b) *Lancet*, ii, 95.
Rossdale, P. D., Mahaffey, L. W. (1958) *Vet. Rec.* **70**, 142.

HEART-DISEASE AND INFLUENZA

GEOFFREY BOURNE
M.D. Lond., F.R.C.P.
PHYSICIAN

JOHN WEDGWOOD
M.D. Cantab., M.R.C.P.
SENIOR REGISTRAR

ST. BARTHOLOMEW'S HOSPITAL, LONDON, E.C.1

A CAUSAL relationship between influenza and heart-disease could be suggested or proved by two methods of observation. A general practitioner, by investigating a large series of influenza cases, might demonstrate it on a statistical basis; or a cardiologist, studying individual cases of heart-disease, might note that the onset appeared to derive from influenza. Either approach is unsatisfactory, for the general practitioner is unlikely to be fully equipped for complete cardiological investigation, and the cardiologist is unlikely to come across a sufficient number of such cases to allow of a firm conclusion; moreover, such a series would be a selected one.

A further difficulty is that influenza cannot be diagnosed exactly unless virological techniques are used.

Historical Review

Three conclusions may be reached from the literature.

1. Rapidly fatal cases of acute myocardial involvement occur in influenza, but are rare. Finland et al. (1945) report two examples in which influenza-A virus was involved:

> In the first case an electrocardiogram (E.C.G.) taken before death showed an atypical low-voltage QRST complex; histology showed a severe diffuse acute myocarditis. The second, with a similar ætiology, showed comparable but less severe histological lesions.

Moreover one of us (G. B.) has clear recollection of a few patients dying of fulminating influenza in 1918 in whom bradycardia (a pulse-rate of 30–40) was observed. One of these was a child.

2. The second conclusion is that in most cases of less severe influenza there is no strong evidence of cardiac involvement. Wood (1941) reported negative clinical and electrocardiographic findings in the epidemic of 1936–37.

3. The third conclusion is that influenza appears to precipitate definite cardiac abnormalities in patients previously suffering from heart-disease.

Cases 5 and 6 in Hyman's series developed gross heart-block following influenza superimposed upon chronic heart-disease (Hyman 1927). Saphir (1941), regarding the subject from the standpoint of pathology, states " It seems clear that myocarditis in so-called grip or influenza is exceedingly rare, though myocardial damage which easily may be interpreted as the result of simple cloudy swelling, may be encountered clinically". Oswald et al. (1958) point out that " Acute myocarditis may have been the precipitating cause of death in a few cases of fulminating influenza, probably resulting more from the general toxæmia than from any specific effect of the virus upon the myocardium. Giles and Shuttleworth (1957), in a series of forty-six postmortem examinations, frequently encountered cardiac enlargement for which there seemed to be no adequate explanation, and myocardial œdema was in their opinion the most constant microscopical finding."

Finally it would seem that complete heart-block is the commonest gross abnormality ascribed to influenza. Auricular fibrillation appears to be rare (Hamburger 1938, Stengel 1918).

The Present Series

In the present series of cases—fourteen in number—observed during the 1957 epidemic, influenza appears to have been the cause of cardiac disability. Auricular fibrillation was precipitated in eight cases and auricular flutter in one. Symptoms of coronary-artery disease were initiated in two cases. Two other patients with angina of effort due to coronary-artery disease, who were being studied by serial exercise tests, became worse after an attack of influenza. Their angina became more severe and objective evidence of their deterioration was obtainable from the exercise tests. Finally in one patient influenza seems to have caused an inversion of the T wave in the left-ventricular leads, but this reverted to normal during convalescence.

Auricular Fibrillation

Case 1.—Mr. A., aged 68. No past history of heart-disease. Bronchitis for 1 year previously, with shortness of breath lasting for 3 weeks. At that time the E.C.G. and cardioscopy were normal. No hypertension was present.

A year later severe attack of febrile upper-respiratory catarrh with bronchitis. Much shortness of breath, both at rest and on slight exertion. No chest pain. Examination shortly afterwards showed no clinical evidence of thyrotoxicosis. Auricular fibrillation present. Blood-pressure 110/74 mm. Hg. E.C.G. normal except for the presence of auricular fibrillation. Heart normal radiologically.

Successfully treated by quinidine sulphate. No recurrence.

Case 2.—Mr. B., aged 55. 12 months previously the heart was found to be normal by his own doctor. 3 weeks previously severe febrile cold with bronchitis. Bed for 9 days. Cardiac irregularity noticed. No evidence of thyrotoxicosis. Heart normal clinically. No murmurs audible. Blood-pressure 136/94. E.C.G. normal except for the presence of auricular fibrillation. Radiologically the heart was within normal limits.

Auricular fibrillation responded to quinidine treatment, but returned 6 months later.

Case 3.—Mr. C., aged 50. Well until he suffered a severe febrile cold. Shortness of breath and palpitation noticed subsequently. On examination no sign of thyrotoxicosis. No murmurs audible. Blood-pressure 120/70. E.C.G. normal except for auricular fibrillation. Radiologically heart not enlarged.

Quinidine treatment tried twice; the first course failed and the second succeeded.

Case 4.—Col. D., aged 58. Perfectly well until 17 days previously. Severe influenza, temperature 105°. Auricular fibrillation noticed. He had previously had short runs of palpitation lasting for seconds only. Since the attack palpitation and cardiac irregularity had persisted. No evidence of thyrotoxicosis. No heart murmurs. Blood-pressure 120/86. E.C.G. showed auricular fibrillation only. Radiologically the heart was normal.

Treated by quinidine successfully: heart regular on maintenance dose.

Case 5.—Mrs. E., aged 46. Perfectly well until 2 weeks previously when she had a severe febrile chest cold. 3 days before examination, sudden onset of palpitation, associated with severe dyspnœa. Heart found to be irregular. No evidence of thyrotoxicosis. No murmurs audible. Blood-pressure 150/90. E.C.G. showed the presence of auricular fibrillation. The QRS complexes were normal. There was some T-wave depression in leads II, III, aVF, and V_7, probably ischæmic in origin. No history of cardiac pain. The heart was normal radiologically.

She refused admission for quinidine treatment. Given maintenance dosage of digitalis.

Case 6.—Mr. F., aged 48. Severe attack of influenza three months before examination. Previously perfectly well. The

respiratory attack was febrile. He was in bed for 4 days. Since then shortness of breath on exertion. No chest pain. No evidence of thyrotoxicosis. No murmurs audible. Blood-pressure 130/86. Auricular fibrillation present. E.C.G. also showed rather flat T waves throughout. No T-wave inversion or ST depression. Radiologically moderate cardiac enlargement. Diagnosis: auricular fibrillation and myocardial degeneration, probably vascular.

Quinidine treatment successful at first, but auricular fibrillation returned and persisted.

Case 7.—Major G., aged 69. Slight chronic bronchitis for years, and 3 years previously an attack of influenza which precipitated auricular fibrillation. This disappeared during convalescence and he remained well.

12 days before examination, severe attack of influenza with fever and cough, heart-rhythm regular. One day previously auricular fibrillation started, proved by E.C.G. No clinical evidence of thyrotoxicosis. No murmurs audible. Blood-pressure 142/72. E.C.G. showed digitalis effect, with some additional T-wave depression in leads II, III, aVF, and V_7. (This change was present 8 months later.) Radiologically no cardiac abnormality. Diagnosis: underlying myocardial degeneration, probably vascular in origin.

Quinidine rapidly restored the normal rhythm. He has remained well, except for transient attacks of auricular fibrillation lasting an hour or so.

Case 8.—Mrs. H., aged 68. A year previously had once experienced slight retrosternal discomfort walking against an East wind. She remained perfectly well until 1 month before examination. She then suffered an attack of febrile upper-respiratory catarrh involving the chest, lasting for a week. Following it she had noticed shortness of breath on exertion, some orthopnœa, slight tightness in the chest on exertion, but no cough. There was no clinical evidence of thyrotoxicosis. She was moderately anæmic (Hb 68%). There was no hypertension. An aortic systolic murmur was audible. The E.C.G. showed auricular fibrillation and some flattening of the T wave in lead I. Radiologically the heart was slightly enlarged. Diagnosis: underlying myocardial degeneration, probably vascular, auricular fibrillation precipitated by influenza.

She was treated symptomatically with digitalis and iron.

Auricular Flutter

Case 9.—Mrs. I., aged 52. For many years slight transitory palpitation from smoking or after parties. Vigorous active normal life. 5 days before examination severe febrile upper-respiratory catarrh with bronchitis. 2 days previously persistent palpitation began. Febrile, sweating, cough. Heart-rate 150, rhythm basically regular, heart-sounds normal, blood-pressure 130/92. Many bronchitic added sounds. E.C.G. showed auricular flutter, auricular rate 300, ventricular rate 150.

Treated by full digitalisation. 8 days later normal regular rhythm. QRST normal except for slight digitalis effect. 8 months later normal active life. No undue shortness of breath or other symptoms. Examinations at patient's house, therefore no cardioscopy.

Coronary-artery Disease

Case 10.—Mr. J., aged 58. Normal activities until influenza 3 weeks previously. Fever for 3 days with bronchitis. 10 days before examination constriction and pain noticed in the left arm walking in the cold at night, disappearing immediately with rest. No prolonged pain. Heart-rate 68, rhythm regular, blood-pressure 122/80. Slight retinal arteriosclerosis. E.C.G. showed T wave flat in lead I and inverted in aVL, late T-wave depression from V_2 to V_5 inclusive. Cardioscopy: transverse diameter 14·0 cm. by orthodiagraph.

3 months later angina of effort much less and only noticed with hurry. No shortness of breath. Physical signs unchanged. E.C.G. showed improvement. T wave normal in lead I, diphasic in aVL, and normal in V_2 and V_5. Very slight late T-wave depression in V_2, T upright but of diminished amplitude in V_4. Cardioscopy: transverse diameter 13·2 cm. by orthodiagraph. (This measurement shows definite diminution in size.)

Case 11.—Mrs. K., aged 52. Well until attack of febrile cold and cough. Since then severe retrosternal pain and tightness on slight exertion, disappearing on rest, radiating to arms —typical of angina of effort. Dyspnœa on exercise. Heart-rate 86, rhythm regular, blood-pressure 148/96. Retinal arteries normal. Slight systolic apical murmur lying. E.C.G. normal except for absent R wave in V_2. Hæmoglobin 98%. Cardioscopy: heart normal in size and shape.

10 months later the retrosternal tightness on exertion was almost negligible.

Case 12.—Mr. L., aged 54 (under the care of Dr. Graham Hayward). Angina of effort and intermittent claudication for $2^1/_2$ years. January, 1957—left-lumbar ganglionectomy. Angina had been mild and not progressive for 1 year. Heart clinically normal. Blood-pressure 140/95. E.C.G.: slight ischæmic ST-segment changes in left-ventricular leads with definite ischæmic changes after exercise. Heart not enlarged on cardioscopy. His progress was being followed by serial and quantitative exercise tests at weekly intervals.

He developed symptoms of influenza on Oct. 7, 1957, and was ill but not in bed for several days. Febrile relapses occurred 10 and 16 days later. Following the first attack his angina became worse and more easily precipitated. He had no pain at rest. The resting E.C.G. was unchanged. Exercise tests gave objective evidence of deterioration.

Case 13.—Mr. M., aged 48. History of angina of effort for 5 years. Heart clinically normal. Blood-pressure 160/86. E.C.G. normal, except for ischæmic ST-segment depression after exercise in V_5. Cardioscopy normal. He was also being studied by serial exercise tests at weekly intervals.

He developed influenza on Oct. 24, 1957, with a febrile relapse 1 week later. He was in bed for several days. Following the infection he complained that his angina was worse. Objective evidence of this was seen in the increased ST depression after the exercise test.

Ætiology Obscure

Case 14.—Mrs. N., aged 70. Had lived an active and vigorous life playing much golf, and occasionally suffering from symptoms caused by premature beats during most of her life. More recently these had developed into short attacks of paroxysmal tachycardia, abolished by prophylactic quinidine sulphate gr. 3 b.d.

She remained in good health until a severe attack of upper-respiratory acute catarrhal infection and sinusitis which developed into a pneumonitis associated with left-pleural pain. Treated with tetracycline for 9 days. On getting up after 2 weeks in bed she noticed distressing and severe shortness of breath on the slightest exertion, associated with palpitation and even faintness. A persistent cough induced by nasal catarrh, and causing slight nausea, bothered her at night. The tetracycline had produced transitory diarrhœa. She was again put to bed.

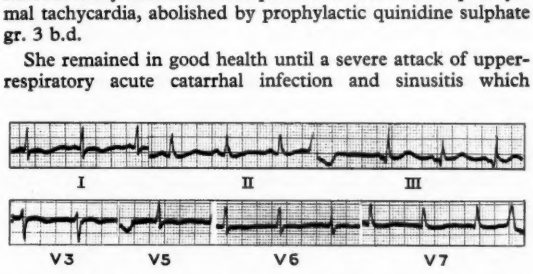


Fig. 1—The influenzal attack started on Aug. 19, 1958. The tracing of Sept. 15 shows T-wave inversion in lead I and from V_2 to V_6 inclusive with flattening of the T wave in V_7.

She was considerably overweight. The heart-rate was 90, rhythm regular except for a few premature ventricular beats.

Normal heart sounds. Blood-pressure 126/80. Physical signs suggested incomplete recovery from left basal pneumonitis. The E.C.G., which had been perfectly normal in all leads a year previously, now showed moderate T-wave inversion in leads I, aVL, and from V_3 to V_7 inclusive (fig. 1.) Chest radiography showed a slightly bulky heart; no evidence of pericarditis; some diminution in translucency of lung bases, no definite consolidation. Full blood-count normal. Blood-urea 30 mg. per 100 ml. Sedimentation-rate 37 mm. in 1 hour (Wintrobe).

Her lassitude and dyspnœa were quickly diminished by rest in bed and treatment with chlorothiazide. $2^1/_2$ weeks later the E.C.G. showed upright T waves in leads I, II, and from V_4 to V_6 inclusive (fig. 2). The T wave in aVL was now diphasic. She

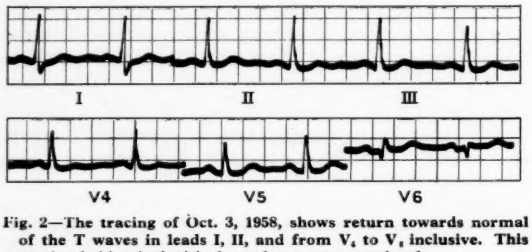


Fig. 2—The tracing of Oct. 3, 1958, shows return towards normal of the T waves in leads I, II, and from V_4 to V_6 inclusive. This tracing is identical with that taken a year previously.

rapidly regained her former exercise-tolerance and became free from dyspnœa.

The most striking clinical point was the very considerable shortness of breath which followed the influenzal attack. There was at no time pain or constriction, suggesting coronary-artery disease, and the E.C.G. remained free from QR abnormalities, or ST deviation.

Conclusions

In four of the eight cases of auricular fibrillation there was no evidence of any other cardiac abnormality; in the four others the E.C.G. revealed signs of an underlying myocardial defect. In the patient with auricular flutter the abnormal rhythm seemed to be due entirely to the acute influenzal infection.

Influenza appeared to initiate angina of effort in two of the four cases with coronary symptoms, and to accentuate the ischæmic state in two. In these latter two cases influenza also increased the electrocardiographic abnormality.

In the last case the long history of premature beats, and later of paroxysmal tachycardia, pointed to some chronic but slight cardiac abnormality.

Thus in six of the fourteen cases influenza would seem to have caused definite cardiac complications, and in the other eight to have brought them to the surface.

The age of the patients, 47–70 with an average of 57, suggests that in all of them the heart may not have been basically perfectly normal.

Influenza appears to have a definite, although transitory, toxic effect upon the myocardium, perhaps—as suggested by Saphir (1941)—by causing cloudy swelling or some lesser change.

REFERENCES

Finland, M., Parker, F., Barnes, M. W., Joliffe, L. S. (1945) *Amer. J. med. Sci.* **209**, 455.
Giles, C., Shuttleworth, E. M. (1957) *Lancet*, ii, 1224.
Hamburger, W. W. (1938) *Med. Clin. N. Amer.* **22**, 111.
Hyman, A. S. (1927) *Arch. intern. Med.* **40**, 120.
Oswald, N. C., Shooter, R. A., Curwen, M. P. (1958) *Brit. med. J.* ii, 1305.
Saphir, O. (1941) *Arch. Path. (Lab. Med.)* **32**, 1000.
Stengel, A. (1918) *Med. Clin. N. Amer.* **2**, 645.
Wood, P. (1941) *Proc. R. Soc. Med.* **34**, 543.

SIDE-EFFECTS OF TETRACYCLINE ALONE AND OF TETRACYCLINE WITH NYSTATIN

R. LARKIN
M.B. Lpool
With the microbiological assistance of
W. W. HESELTINE, F.P.S., M.I.BIOL.

TETRACYCLINE probably remains the most dependable drug for the treatment of the acute " flare-up " of chronic non-specific respiratory infections encountered in practice; but distressing side-effects are fairly common. Childs (1956) found that nystatin inhibited the increased growth of *Candida albicans* observed in the fæces of patients treated with tetracycline, but there is disagreement about the ability of nystatin to modify the incidence of gastrointestinal and other side-effects caused by tetracycline. For example, Stone and Mersheimer (1955–56) and Robinson (1957–58) reported that such side-effects were much reduced by the addition of nystatin, whereas Hewitt et al. (1955–56) observed that when nystatin was administered with the tetracycline the incidence of side-effects was much the same as when tetracycline alone was administered.

Materials and Methods

A total of 98 adult patients, mainly with acute or chronic respiratory infections, were placed at random in two groups. Those in one group were treated with 250 mg. of tetracycline hydrochloride four times daily, and those in the other group with 250 mg. of tetracycline hydrochloride with 250,000 units of nystatin four times daily.

Clinical side-effects were recorded in terms of gastrointestinal discomfort, diarrhœa, and anogenital pruritus; and in the latter part of the trial rectal and throat swabs were taken on the fifth day of treatment and examined for the presence of *C. albicans* and other yeasts. The mycological tests were conducted on code-labelled swabs so that the form of treatment was not divulged. Swabs were examined by the usual methods of identifying *Candida* species (Benham 1957) and by means of Nickerson's medium (Hengerer and Covert 1956) and Pagano-Levin medium (Pagano et al. 1957–58).

Results

The clinical side-effects observed in the two groups of patients are shown in table I. In this trial tetracycline produced side-effects more commonly than the tetracycline-nystatin combination.

Among the gastrointestinal disturbances, a sensation of abdominal distension was common. Nausea and vomiting

TABLE I—CLINICAL SIDE-EFFECTS

Side-effect	Tetracycline group: 55		Tetracycline-nystatin group: 43	
	No.	%	No.	%
Gastrointestinal disturbances	37	67	4	9
Diarrhœa	9	16	0	0
Anogenital pruritus	13	24	2	5

TABLE II

Side-effect	No. of patients	*C. albicans* isolations		Other yeast isolations	
		Rectum	Throat	Rectum	Throat
Tetracycline group (19):					
Distension and general gastrointestinal discomfort	16	6	13	4	1
Nausea or vomiting	4	1	4	1	..
Frank diarrhœa	5	2	2	2	..
Anogenital pruritus	7	5	6	1	..
None	3	2	2	1	1
Tetracycline-nystatin group (18):					
Distension and general gastrointestinal discomfort	1	1	1	..	..
Nausea or vomiting	..	..	..	..	..
Frank diarrhœa	..	..	..	..	..
Anogenital pruritus	..	..	..	..	..
None	17	..	6	1	6

were less frequent, and the side-effects mainly involved the lower intestinal tract, rather than the upper gastro-intestinal region.

The relation of side-effects to the isolation of *C. albicans* and other yeasts in a total of 37 cases in shown in table II.

Although *C. albicans* and other yeasts were isolated from rectal and throat swabs taken from patients showing no evidence of gastrointestinal side-effects or moniliasis, positive cultures were more often found in those who complained of the side-effects described. The nystatin component apparently had an inhibitory effect on yeasts in the throat, although it was less pronounced than that on the fæcal organisms. Of the 37 patients investigated microbiologically, 3 developed oral thrush; and, in these 3, who received tetracycline alone, *C. albicans* was found in all the throat swabs and in 2 of the rectal swabs.

No attempt was made to identify systematically the yeasts other than *C. albicans*. In the total of 74 positive and negative cultures good correlation was found between the results obtained with Pagano-Levin medium and those of standard identification tests, although in 7 instances the colonies on the medium were indefinite until the sixth or seventh day of storage at room-temperature (average about 17°C). In 6 of these instances the organisms proved to be yeasts other than *C. albicans*, and the 7th was a mixed culture of *C. albicans* and other yeasts. The results obtained with Nickerson's medium agreed with the other findings in 58 of the 74 cultures. In 3 instances this medium showed no organism when *C. albicans* was present, while the other disagreements were associated with the presence or absence of fungi other than *C. albicans* and may therefore be inconsequential. Colonies indicating *Candida* species did not appear on Nickerson's medium in 3 cases until the ninth day of storage at room-temperature.

Discussion

In this trial, gastrointestinal side-effects were much commoner when tetracycline hydrochloride was given alone than when the same dose was administered with nystatin. Since nystatin is antifungal and has little effect on bacteria, viruses, and various animal cells, it seems reasonable to assume that suppression of fungi is responsible for the reduction in side-effects. This assumption is supported by the frequent isolation of *C. albicans* and other yeasts from rectal and throat swabs taken from patients who complained of gastrointestinal disturbances. The simultaneous administration of nystatin with tetracycline inhibits the overgrowth of fungi in the intestines and has a similar, although less pronounced, effect on yeasts in the throat. In addition to affording protection against the direct invasion of tissue by *C. albicans* leading to clinical moniliasis, nystatin apparently can reduce substantially gastrointestinal disturbances during the oral use of tetracycline hydrochloride, which may be fungal hypersensitivity reactions.

Summary

98 patients suffering mainly from acute or chronic respiratory infections were divided at random into two groups, of which one (55 patients) was given 250 mg. tetracycline hydrochloride four times daily and the other (43 patients) 250 mg. tetracycline hydrochloride and 250,000 units nystatin four times daily.

Gastrointestinal disturbances were noted in 37 of the 55 patients on tetracycline alone, and in 4 of the 43 on tetracycline plus nystatin. Diarrhœa developed in 9 of the former group but in none of the latter group. On the fifth day of treatment rectal swabs positive for yeasts were obtained from 11 out of 19 tetracycline-treated patients and from 2 out of 18 given the tetracycline-nystatin combination. Oral thrush developed in 3 of the 19 patients given tetracycline alone but in none of the 18 who received nystatin in addition.

REFERENCES

Benham, R. W. (1957) *J. chron. Dis.* **5**, 460.
Childs, A. J. (1956) *Brit. med. J.* i, 660.
Hengerer, A. D., Covert, S. V. (1956) *G.P.* **13**, 88.
Hewitt, W. L., Finegold, S. M., Sutter, V. L. (1955–56) *in* Antibiotics Annual; p. 856. New York.
Pagano, J., Levin, J. D., Trejo, W. (1957–58) *ibid.* p. 137.
Robinson, M. M. (1957–58) *ibid.* p. 451.
Stone, M. L., Mersheimer, W. L. (1955–56) *ibid.* p. 862.

MYOCARDIAL INFARCTION IN A HÆMOPHILIAC

CHR. F. BORCHGREVINK
M.D. Oslo

From the Institute for Thrombosis Research, University Hospital (Rikshospitalet), Oslo, Norway

Boivin (1954) reported a case of myocardial infarction in a mild hæmophiliac. Three years later Stewart and Acheson (1957) described a case of widespread atherosclerosis involving the coronary arteries in a hæmophiliac.

Because such cases may shed light on the pathogenesis of atherosclerosis (Duguid 1955, Astrup 1957), and raise interesting questions regarding therapy, the following case is presented.

Case-report

The patient was a 68-year-old man. His family tree is shown in fig. 1. His abnormal bleeding tendency was discovered at the age of 25 after extraction of a tooth: he started to bleed next day and went on bleeding for two weeks. He has had similar experiences several times since then.

At 27, and again at 34, he was admitted to Rikshospitalet, Oslo, because of melæna. No cause for this was found: his bleeding-time and whole-blood clotting-time were reported as normal. At 57 he underwent two minor operations. Both times bleeding began a day or two after surgery and continued until controlled by blood-transfusion.

He has never had bleeding into the joints, epistaxis, or hæmaturia. After trivial cuts bleeding has always stopped normally.

At 65 he was readmitted to Rikshospitalet because of his bleeding tendency. Except for a slightly prolonged cephalin-time (Waaler 1957), all tests of his hæmostatic mechanism gave normal results. No definite diagnosis was made.

Since the age of 58 he has had angina pectoris—retrosternal pain on exertion which has responded to nitroglycerin. At the beginning of last July he developed a more constant retrosternal pressure; and nitroglycerin became less effective. He was again admitted to Rikshospitalet on July 16 with impending infarction. During the first night in hospital he had a typical posterior-wall infarction: his electrocardiogram is shown in fig. 2. Routine treatment with heparin and phenindione (P.I.D.) for the first days, followed by P.I.D. alone, was started immediately. As soon as his hæmorrhagic diathesis was diagnosed the P.I.D. was discontinued.

After the first two or three days of rather severe retrosternal pain he made a speedy recovery; and he was discharged after four weeks.

His hæmostatic mechanism was investigated during a period when he was not on heparin and P.I.D., and the results are presented in the table. These clearly point to a diagnosis of mild hæmophilia A.

Discussion

The ten-year history of angina pectoris, the sudden onset of a longer episode of retrosternal pain, and the abnormal electrocardiogram provide unequivocal evidence of myocardial infarction. The history of a tendency to secondary bleeding is typical of mild hæmophilia; and so

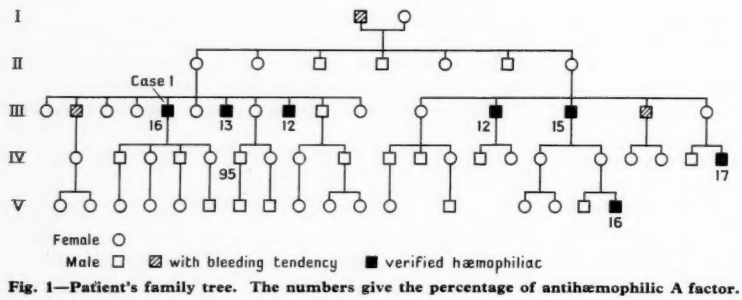


Fig. 1—Patient's family tree. The numbers give the percentage of antihæmophilic A factor.

are the laboratory findings of a prolonged secondary-bleeding-time and a slightly prolonged cephalin-time. A specific test, which makes use of plasma from a known severe hæmophiliac as substrate, showed an antihæmophilic A factor (factor-VIII) level of 16%. The family tree, moreover, shows that six of his male relatives have hæmophilia, the levels of their antihæmophilic A factor varying from 12% to 17%. Thus, as is characteristic of hæmophilia, not only the anomaly itself but also its severity is inherited.

So far as I know, this is only the third reported case of myocardial infarction in a hæmophiliac. Does this mean that severe hæmophiliacs do not reach the age of infarction? Does it mean that mild hæmophilia often goes undiagnosed? Or does it mean that hæmophilia protects against myocardial infarction? So long as we do not know the prevalence of the combination of infarction and hæmophilia in proportion to the prevalence of each disease in the various age - groups we cannot give the answer. The reported cases demonstrate only that hæmophiliacs are not completely protected against myocardial infarction.

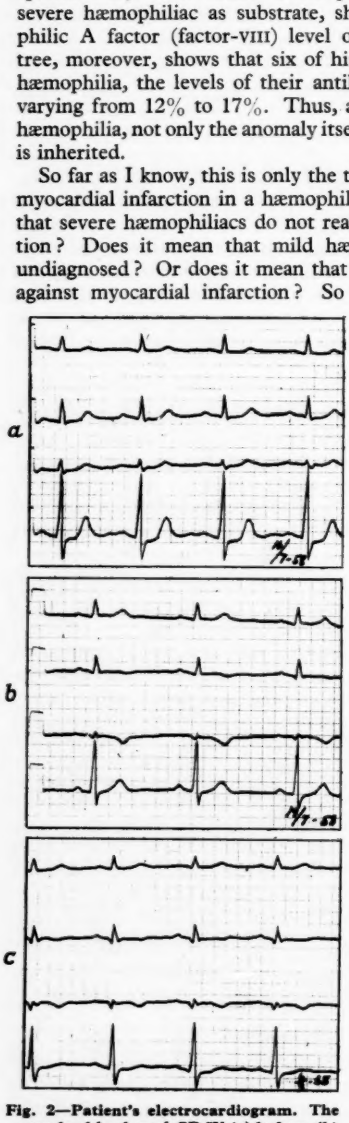


Fig. 2—Patient's electrocardiogram. The standard leads and CR IV (a) before, (b) the day after, and (c) three weeks after myocardial infarction.

Even if it is impossible to prove that the infarction in this patient was not caused by intimal bleeding, the ten-year history of typical angina pectoris certainly points to progressive coronary sclerosis.

The case also raises the question whether mild hæmophiliacs who develop myocardial infarction should be put on anticoagulant treatment, temporarily or permanently? Dicoumarol and related drugs reduce the blood-levels of four clotting factors—prothrombin, proconvertin, Stuart-Prower factor, and antihæmophilic B factor. It may well be that the combined reduction of these four factors offers better protection against infarction than the reduction of only the antihæmophilic A factor. However, we know nothing of the frequency of bleeding in mild hæmophiliacs on anticoagulants. One possibility might have been to put this patient on P.I.D. treatment, keeping his prothrombin-proconvertin level at about 50%; but we have no evidence that this would have given him any protection. It was therefore decided as soon as the diagnosis of hæmophilia was made that the P.I.D. should be discontinued.

LABORATORY TESTS OF PATIENT'S HÆMOSTATIC MECHANISM

Test	Results in patient	Normal range	Reference to method
Bleeding-time ..	7 min.	3–11 min.	Borchgrevink and Waaler (1958)
Secondary-bleeding-time	12 min.	2–6 min.	Borchgrevink and Waaler (1958)
Whole-blood clotting-time	4 min.	2–5 min.	Hjort and Stormorken (1957)
Tourniquet test ..	2 petechiæ	0–20 petechiæ	Stefanini and Dameshek (1955)
One-stage thromboplastin-time	12·5 sec.	12–13 sec.	After Quick, using human instead of rabbit brain
Prothrombin and proconvertin	91%	80–120%	Owren and Aas (1951)
Cephalin-time:			
(*a*) First threads ..	48·6 sec.	35–40 sec.	Waaler (1957)
(*b*) Firm clot ..	67·5 sec.	50–60 sec.	Waaler (1957)
Prothrombin ..	85%	80–120%	Hjort, Rapaport, and Owren (1955)
Proconvertin ..	88%	70–130%	Aas (1952)
Proaccelerin	105%	70–150%	Aas (1952)
Antihæmophilic factor A	16%	75–125%	Waaler (1959)
Antihæmophilic factor B	98%	75–125%	Stapp (1958)
Fibrinogen	280 mg. per 100 ml.	200–400 mg. per 100 ml.	..
Fibrinolysis	—	..	Astrup and Müllertz (1952)
Thrombocytes per cmm.	251,000	150,000–300,000	Nygaard (1933)
Adhesive thrombocytes per c.mm.	135,000	60,000–160,000	Hellem (1958)
Adhesive thrombocytes %	53·9	35–60	Hellem (1958)
Clot retraction ..	Normal	..	Voss (1958)

Summary

A case of myocardial infarction in a mild hæmophiliac is reported. Possible reasons for the apparent rarity of this combination of illnesses are considered. The question whether or not such patients should have anticoagulant treatment is raised.

My thanks are due to Prof. P. A. Owren, head of the Institute for Thrombosis Research, who kindly read the manuscript.

REFERENCES

Aas, K. (1952) Prokonvertin og Konvertin. Thesis, Oslo.
Astrup, T. (1957) *Lancet*, ii, 745.
— Müllertz, S. (1952) *Arch. Biochem. Biophys.* **40**, 346.
Boivin, J. M. (1954) *Arch. Mal. Coeur.* **47**, 351.
Borchgrevink, C. F., Waaler, B. A. (1958) *Acta med. scand.* **162**, 361.
Duguid, J. B. (1955) *Brit. med. Bull.* **11**, 36.
Hellem, A. (1958) *Int. Congr. Hæmat.* paper 313. Rome.
Hjort, P., Rapaport, S. I., Owren, P. A. (1955) *Scand. J. clin. Lab. Invest.* **46**, 89.
— Stormorken, H. (1957) *ibid.* **9**, suppl. 29.
Nygaard, K. K. (1933) *Proc. Mayo Clin.* **8**, 365.
Owren, P. A., Aas, K. (1951) *Scand. J. clin. Lab. Invest.* **3**, 201.
Stapp, W. (1958) *ibid.* **10**, 169.
Stefanini, M., Dameshek, W. (1955) The Hemorrhagic Disorders. New York.
Stewart, J. W., Acheson, E. D. (1957) *Lancet*, i, 1121.
Voss, D. (1958) *Int. Congr. hæmat.* paper 443. Rome.
Waaler, B. A. (1957) *Scand. J. clin. Lab. Invest.* **9**, 322.
— (1959) *ibid.* (in the press).

AN ALARMING SIDE-EFFECT OF TOFRANIL

H. L. ENGLISH
M.B. Cantab., M.R.C.P., D.P.M.
SENIOR HOSPITAL MEDICAL OFFICER, DEVA HOSPITAL, CHESTER

'TOFRANIL' (known in the United States as 'Imipramine'), which chemically is N-(γ-dimethylaminopropyl)-iminodibenzyl hydrochloride, was introduced to this country in January, 1959, for the treatment of depression, and is at present only supplied to hospitals. Clinical trials have been reported by Azima and Vispo 1958, Keilholz and Battegay 1958, Kuhn 1958, and Lehmann et al. 1958. The oral dosage recommended by the manufacturers is 100 mg. in divided doses on the first and second days, increasing by 50 mg. daily to 250 mg. After a week or so at this level, the dose is gradually reduced to a maintenance level depending on the patient's response.

The drug has been found to produce a number of side-effects, mostly of a mild nature, such as an atropine-like syndrome, parkinsonism, disturbances of the peripheral circulation, hypotension, and occasionally allergic reactions. But the effect which I now describe has not been mentioned previously, and I hope that others may be able to avoid it.

This drug seemed likely to be useful in cases where electroconvulsive therapy (E.C.T.) was inadvisable or impossible—for example, because of poor general condition, arteriosclerosis, or when permission was refused. A preliminary trial was therefore started on six patients. Five were over 70, and three developed symptoms soon after the dose of tofranil reached 250 mg. daily. During the day before, the patient complained of being a little tremulous, but showed only slight cogwheel rigidity.

The reaction itself was sudden, starting with a coarse tremor of all four limbs similar to the intention tremor of cerebellar ataxia except that it was little affected by attempts at voluntary movement and was present at rest. No other relevant neurological signs were found, but, because of the tremor, the patients were unable to stand and fell down. One patient (case 4) fractured the neck of her left femur. On discontinuing tofranil, the effects passed off in about 72 hours, and the drug could then be given again in a lower dosage. The reaction was not caused by giving tofranil and chlorpromazine together.

Case-reports

Case 1.—A woman of 76, with chronic melancholia, who had been in hospital for 2 years, had previously attempted suicide and was still thought to be potentially suicidal. She was hypertensive with an enlarged heart. In December, 1958, she was found to have slight weakness of the left side with increased reflexes but there was no history of a stroke. She was therefore considered unfit for E.C.T., and was given tofranil. On the 7th day she developed generalised tremor and fell down without injuring herself. She was put to bed, and the drug was stopped. The tremor then subsided, and 4 days later tofranil was given again in a dose of 200 mg. daily. As there was a mild recurrence of the tremor, the dose was rapidly reduced to 150 mg. It was kept at this level without further tremor, but with little alleviation of her depression.

Case 2.—A woman of 72 had been in hospital for 7 months. She was depressed and hypochondriacal, and she gave a history of a stroke some 6 months before admission. This had left no paralysis, but there was slight exaggeration of reflexes on the right side. She was therefore thought to be unfit for E.C.T., and was given tofranil. On the 3rd day she was somewhat drowsy, but gave no cause for alarm until the 6th day when she developed a generalised tremor and fell without injuring herself. Tofranil was discontinued, but it was started again 5 days later, when the tremor had subsided, in a dose of 200 mg. This was soon reduced to 150 mg., but even then she was inclined to tremble, and the dose was reduced further to 125 mg. The depression has been slightly alleviated.

Case 4.—A woman of 73 had been severely depressed for some 2 years before her admission to hospital. She was then in a very poor and emaciated physical state. After she had been in hospital several weeks and her condition had improved, E.C.T. was offered but she refused this treatment, and was therefore given tofranil. On 250 mg. daily she was slightly shaky, and, in view of the previous experiences, the dose was reduced to 200 mg. on the 8th day, and 175 mg. on the 11th day. That evening, however, she developed a generalised tremor and fell twice while being taken to bed. The second time she fractured her left femoral neck. Tofranil was discontinued for 3 days, then given again in a dose of 100 mg. On this her depression has gradually improved although she is confined to bed.

A further patient (case 5) might have developed this syndrome had the dosage of tofranil not been reduced, but such a reduction did not prevent the reaction in case 4.

These examples suggest that treatment should be more cautious in the older patient, particularly if organic changes are suspected.

Summary

A generalised tremor arose in three of the first six cases treated with 'Tofranil'. These patients were all over 70.

The reaction was alarming in that the onset was sudden and the patients fell, one sustaining a fracture. The tremor cleared rapidly when tofranil was stopped, and treatment was then continued on a lower dosage.

I wish to thank the Geigy Pharmaceutical Company for supplying the 'Tofranil'.

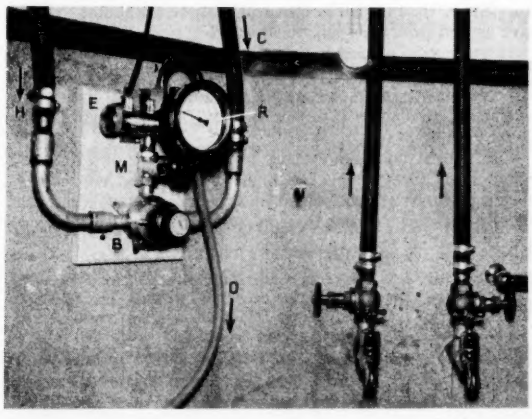
REFERENCES

Azima, H., Vispo, R. H. (1958) *Amer. J. Psychiat.* **115**, 245.
Keilholz, P., Battegay, R. (1958) *Schweiz. med. Wschr.* **88**, 763.
Kuhn, R. (1958) *Amer. J. Psychiat.* **115**, 459.
Lehmann, H. E., Cahn, C. H., de Verteuil, R. L. (1958) *Canad. psychiat. Ass. J.* **3**, 155.

New Inventions

CONTROL OF TEMPERATURE IN REWARMING BLANKETS DURING HYPOTHERMIA

AFTER hypothermia has been induced by surface cooling, it is usual to place the patient between two layers of a rewarming blanket through which water at a few degrees above body temperature is circulating. The apparatus described here is designed to provide a continuous flow of water at any desired temperature, for as long as required, without employing pumps or reservoirs (which take up valuable space). Also it introduces two safety factors.



The hot and cold water feeds are led in as shown to a 'Leonard Water-Blender' (B). The resulting mixture passes upwards through a master control valve (M) to a 'Rototherm' thermometer (R) and thence by the outlet tube (O) to the re-warming blanket. The temperature of the water as shown on (R) is controlled by turning the knurled head of (B) towards the hot or cold position. As the blender can be affected by gross variations in water pressure, and as at least one blanket on the market can be used only at a water pressure not exceeding 5 lb., it is necessary to have a fixed head of pressure. This is achieved by having two small tanks fitted in the roof at approximately $11\frac{1}{2}$ ft. above the blanket level. These are of the automatic ball-valve type (capacity 15 gallons each) and can be fed directly from the nearest hospital hot or cold mains supply as shown. With these tanks fitted, the master control and the two cocks on the taps are left fully open throughout. With a constant head of pressure, the temperature of the water issuing from the blanket does not vary more than $\pm 1°C$.

The second safety factor is shown at E. It consists of a thermostatically controlled switch (on mains voltage) connected to two warning lights fitted up in parallel close to the spot where the anæsthetist is working. The switch in use at the North Middlesex Hospital is set to light up the lamps at 44°C. This switch is not likely to come into operation unless there is some mechanical interference with the cold water supply to the blender, but it is a comforting safeguard.

All junctions of piping or tubing must be airtight, because any entrainment of air can upset the water-blender.

The illustration shows how the equipment can be set up without using an expensive installation, but obviously a more elaborate finish could be achieved if required.

I am indebted to Mr. P. C. Vedast, superintendent engineer, for his many helpful suggestions and for obtaining the various parts. My thanks are also due to Mr. J. B. Petter, senior engineer, for superintending the installation and for his unfailing patience in getting everything "just right".

The 'Leonard Water-Blender' is manufactured by Walker, Crossweller, & Co. Ltd. The 'Rototherm' is supplied by British Rototherm Co. Ltd. The electric thermostat is made by Electro-Methods Ltd.

North Middlesex Hospital, London, N.18

G. S. A. KNOWLES
M.B. Lond., F.F.A. R.C.S.

Reviews of Books

Medical History of the Second World War

The Army Medical Services. Campaigns: Vol. III. F. A. E. CREW, F.R.C.P.E., F.R.S. London: H.M. Stationery Office. 1959. Pp. 645. 100*s*.

THIS book, which deals with the war in Sicily and Italy and the second venture in Greece, follows the plan of its predecessors. Each phase of the campaigns is dealt with separately: the strategic plan, the activities and moves of the medical units in relation to the tactical manœuvres of the armies, the medical problems of special interest, and an ample statistical analysis. Those who will enjoy it most are those who followed the drum from the rather haphazard landing in Sicily to the peaceful ending in Venice or Carinthia; but there are lessons here for everyone. In Sicily malaria was a more dangerous enemy than Germans or Italians and at one time disaster was not far away: regrettably, occasional catastrophes seem needed to make the doctor's voice heard in the councils of war. In Naples typhus was the danger but this was a problem for AMGOT rather than for the Army. The evacuation of casualties from Anzio taught much that was useful on the beaches of Normandy. Of more lasting value was the mass of detailed observations assembled by the Consultant Surgeon on the best treatment of wounds in men who must be carried a long way before they reach hospital: at one time the L. of C. were over 200 miles long and much of the going was very rough. Now that many of our ambulance services are under the immediate control of laymen it is worth remembering that for some kinds of injuries an ambulance ride is very often fatal. The sulphonamide-resistant gonococcus appeared to dispel medical (but not lay) optimism and gave us a warning of similar problems to come. The field ambulance, the pet of the R.A.M.C., disclosed failings which have caused headaches at Crookham ever since, but ingenious improvisations (discussed in detail) served their purpose. The Italian partisans had hygienic failings which were difficult to remedy because rank was so valued in the army of the cobelligerents that no M.O. would think of speaking his mind to the colonel.

The author does not belong to that school of historians who hold that history should stir the deeper emotions, but this book is packed with facts which must be recorded. We must be grateful that this has been done in an orderly and lucid fashion.

Suicide in Hong Kong

With Special Reference to Attempted Suicide. P. M. YAP, M.A., M.D., M.R.C.P.E., honorary lecturer in psychiatry, University of Hong Kong. Hong Kong: Hong Kong University Press. London: Oxford University Press. 1959. Pp. 101. 12*s*. 6*d*.

INTEREST in suicide as a sociological correlate dates back over sixty years, but little of the great amount of work that has been done was concerned with less well-developed countries. Dr. Yap's careful studies in Hong Kong are therefore welcome. The 263 suicides and 1418 attempts took place between 1953 and 1955 (some figures dating from 1946 are also given) and all except 3 involved Chinese. The factual part of this book lately appeared elsewhere.[1]

It is interesting to note how the patterns of suicide differ in this compact but changing society from those of "americanised" Chinese communities, which resemble the Western world in incidence-rates, and from those of the traditional Chinese culture where veneration of the elderly apparently has a protective effect. Although the reliability of some of the data must be a little suspect, it is striking that mental illness unrelated to immediate stress was thought to be as low as 2·5% and 7·8% for attempted and successful suicide cases, and that the peak period in the year does not coincide (as it usually does) with the peak of mental-hospital admissions. Broadly, however, the usual correlates of social disorganisation, the unmarried state, poverty, &c., hold good. Dr. Yap is to be congratulated on a valuable thesis.

Recent Advances in Respiratory Tuberculosis (5th ed. London: J. & A. Churchill. 1959. Pp. 284. 35*s*.).—When the 4th edition of this book was published ten years ago, chemotherapy was hardly out of the experimental stage, pneumothorax was very popular, lung resection rapidly developing, B.C.G. vaccination a subject of almost emotional controversy, and village settlements and rehabilitation matters of great moment. Now chemotherapy can be widely, rationally, and effectively used, pneumothorax treatment has almost ceased, resection has passed its peak, B.C.G. is respectable, and settlements and rehabilitation of relatively little importance. So the book has been rewritten, not merely revised, by Prof. Frederick Heaf and Dr. N. Lloyd Rusby. As so much of the theory and practice of ten years ago is now obsolete, "recent advances" have become accepted everyday ideas; and the book is, therefore, more of a textbook than a refresher course. It would be stupid to dismiss as valueless all articles on tuberculosis published before 1945. Much of the experimental work, for instance, was of great importance and high quality, as were some of the epidemiological field studies; but it is revealing to see in this book what a satisfactory account of respiratory tuberculosis in all its aspects can be derived from the published work since 1950, for few of the references are from earlier years. Admittedly, recent work is built on the foundations of previously acquired knowledge, but, particularly in regard to treatment and other matters of clinical observation, the papers of the past ten years do show a greater appreciation of the principles of logical inference: the testing of evidence is more prominent than the uncritical acceptance of impressions, and reason is replacing dogma. This book presents the evidence fairly and as fully as possible in the space. It is refreshingly free from shibboleth and deserves wide circulation.

1. Yap, P. M. *J. ment. Sci.* 1958, **104**, 266.

THE LANCET

LONDON 13 JUNE 1959

Hodgkin's Disease

A HUNDRED AND THIRTY years ago HODGKIN, BRIGHT, and ADDISON were contemporaries at Guy's Hospital; but if they were able to return now, only ADDISON would have the satisfaction of finding that real progress has been made in discovering the causes and effective treatment of the syndromes named after them. Hodgkin's disease has always aroused great interest, particularly because it develops mainly in patients aged between 20 and 40, whose incapacity or death is a serious matter for their families and the community. But, although much has been written, it is fair to say, as ROTTINO [1] does, that "research in Hodgkin's disease, except for the early work in pathology and the discovery of the ameliorative effects of X-rays and mustard compounds, had been frustratingly sterile". A big difficulty has been that no comparable disease is found in animals. GORDON [2] made extracts of lymph-nodes affected by Hodgkin's disease, and showed that these extracts injected intracerebrally into guineapigs caused fatal encephalitis in two-thirds of the animals. But this effect is now attributed to the eosinophils present in the tissue; it is not thought to be specific for Hodgkin's disease. BOSTICK [3] says that there is some evidence that Hodgkin's disease is caused by a virus; this evidence, though admittedly still only circumstantial, is growing. ROTTINO [1] believes that the clue will be found in the nature and cause of the changes that transform a reticuloendothelial cell into a Sternberg-Reed giant cell. In his opinion the lymphocyte and eosinophil hyperplasias represent reactive phenomena. While these fundamental researches make slow progress, the clinician is dealing more effectively than formerly with diagnosis, prognosis, and palliative treatment.

Diagnosis still rests primarily on finding characteristic histological changes in biopsied tissue, and we have learnt to distinguish the other syndromes, such as follicular lymphoreticulosis (Brill-Symmers syndrome), which give rise to a similar clinical picture but which may need different treatment. The type of histological change in the tissues has been used to gain some clue to prognosis; thus the "paragranuloma" [4] type of change is thought to point to a reasonably good prognosis, whereas the presence of many giant cells in mitosis and signs of much reticulum-cell activity signify that a malignant phase may have set in and that the clinical course will be short. But most clinicians consider that a clinical classification gives a better guide to prognosis and is more useful in deciding on treatment. Both DIAMOND [5] in the U.S.A. and WARWICK and SELLERS [6] in Canada use this type of classification in their recent surveys; they divide cases into three classes: in class I the disease is limited to a single area, and there are no constitutional symptoms and signs; in class II two or more lymphatic areas are involved in a single anatomical region, (*a*) without and (*b*) with constitutional symptoms and signs; in class III several anatomical areas are involved and constitutional symptoms and signs are serious. WARWICK and SELLERS show that the four-year survival in a group of 411 cases was about 60% for class I, 45% for class II(*a*), 35% for class II(*b*), and under 20% for class III.

DIAMOND reviewed the cases of Hodgkin's disease seen in 1918–53 at the Memorial Center for Cancer, New York; some 2500 cases were recorded under this diagnosis, but in about 500 there was no histopathological report, and in many others the recorded data were inadequate; eventually 713 cases were collected that had adequate clinical records, with sections of pathological material by which the diagnosis was confirmed, and with adequate records about treatment. The incidence was highest in young adults: half of the patients were aged 20–39; but 11 were under 9 years old, and 21 were over 70 at the time of diagnosis. The five-year survival-rates were 20·5–22·7% in those aged 10–49 years, and somewhat less in other groups; the ten-year survival-rate was just under 10% at the best. These figures are low, but DIAMOND points out that more than 50% of patients with Hodgkin's disease seen at the Memorial Center for Cancer first attend there when they are already in an advanced stage and have received initial treatment elsewhere. WARWICK and SELLERS based their review on the records of 960 patients diagnosed as having Hodgkin's disease and attending the cancer clinics in Ontario between 1932 and 1951; slides relating to 547 cases were available for review, and 422 of these were accepted as Hodgkin's disease, the others being classified as various types of "malignant lymphoma". Both surveys draw attention to the long survival of a minority of patients. WARWICK and SELLERS say reasonably that, though "one-third of patients with Hodgkin's disease die within a year of diagnosis, those who survive to the five-year and especially the ten-year mark have increasingly favourable prognosis." Accordingly, treatment should be carefully considered.

The forms of treatment are two: radiotherapy and chemotherapy. Chemotherapy has been developed only in the past fifteen years, and consequently most patients in long-term surveys have received some radiotherapy, and some have received combined radiotherapy and chemotherapy. Surgery is practically limited to the removal of an isolated group of enlarged lymph-glands in the neck. Chemotherapy involves the administration of alkylating substances, the most potent being nitrogen mustard and some of its modifications such as chlorambucil. Folic-acid antagonists, corticosteroids, and some antibiotics such as actinomycin C have been tried without success. In DIAMOND's group all 713 patients

1. Rottino, A. *Ann. N.Y. Acad. Sci.* 1958, **73**, 4.
2. Gordon, M. H. *in* Rose Research in Lymphadenoma; p. 7. Bristol, 1932.
3. Bostick, W. L. *Ann. N.Y. Acad. Sci.* 1958, **73**, 307.
4. Harrison, C. V. *J. Path. Bact.* 1952, **64**, 513.
5. Diamond, H. D. *Ann. N.Y. Acad. Sci.* 1958, **73**, 357.
6. Warwick, O. H., Sellers, A. H. *Canad. med. Ass. J.* 1959, **80**, 423.

received radiotherapy, and 155 had one or more courses of chemotherapy as well; but the effect of combined treatment was not fully assessed except in paraplegia associated with epidural Hodgkin's disease. In this condition DIAMOND et al.[7] found that, whereas radiotherapy alone restored motor and sensory function in 50% of patients, 90% were relieved by combined radiotherapy and chemotherapy. WARWICK and SELLERS also use radiotherapy alone in most cases: of 417 treated patients, 326 had radiotherapy alone, 59 had combined therapy, and only 1 had chemotherapy alone. The Canadian workers use chemotherapy only " where the extent of the disease makes radiotherapy impracticable or where radiotherapy seems to have no further useful part to play in the management of the disease ". This accords with the orthodox view, which is strengthened by improvements in radiotherapy, such as million-volt X rays [8]. But, though chemotherapy has not yet such long lists of treated patients to its credit, its advantages are leading to its increasing use, and great efforts are being made to find easily administered and reliable drugs which act like the original nitrogen mustard. FARBER [9] states that 45,000 chemical compounds and " antibiotic beers " have been tested by the Cancer Chemotherapy National Program in the U.S.A. WILKINSON [10] in Manchester has treated 80 cases of Hodgkin's disease with nitrogen mustard and obtained complete regression of enlarged lymph-glands in 83% and of spleen in 76%; survivals of up to eleven years have already been recorded. Good remissions have also been recorded with other drugs such as thiotepa and chlorambucil. These drugs are simple to administer and control in the outpatient clinic, and no elaborate installations are required. They will undoubtedly be used increasingly as time goes on and experience is gained with them, particularly as there is increasing reluctance to expose to high doses of X rays a patient who may survive for many years.

Pulmonary Syndrome in the Newborn

RESORPTION atelectasis, in combination with hyaline-membrane formation, intrapulmonary hæmorrhage, or pulmonary œdema, was described by BOUND et al.[11] as " pulmonary syndrome of the newborn ". This condition is perhaps better known as " hyaline-membrane disease ", but BOUND and his colleagues were careful to point out that the clinical picture in cases of atelectasis with œdema or hæmorrhage could be similar to the picture in cases where a hyaline membrane is found on histological examination. Other investigations have also pointed to the importance of atelectasis and have placed less emphasis on membrane formation.[12]

It now seems probable that this pulmonary disorder is not confined to the human species. In this issue Mr. MAHAFFEY and Mr. ROSSDALE describe a convulsive syndrome in newborn foals which has features in common with that found in the newborn infant.

The animals appear to be quite well immediately after birth but then show respiratory distress followed by violent convulsions. Recovery is to be expected in about half the cases when an accurate diagnosis is made and the foals are carefully nursed. In the fatal cases the lungs have the appearance and consistence of liver and the ductus arteriosus is unusually wide. On histological examination the lungs show resorption atelectasis, and in two cases hyaline membrane formation has been noted. One curious lesion seen in these foals is the poor cellularity, or even hyaline degeneration, of the malpighian bodies in the spleen. This has no parallel among the human cases except for general poor development of the malpighian structures in the very immature infant.

The main difference between the disorder in the foal and in the human is the fact that in the foal it does not seem to be related to prematurity. What seems especially interesting is the fact that the only foals affected are thoroughbreds born indoors; the disease has not been reported in animals born under natural conditions. MAHAFFEY and ROSSDALE point out that the foals born indoors may lose as much as 30% of their blood-volume compared with those delivered in their normal surroundings, and they suggest that this lowering of the blood-volume is a factor in causing the lung abnormalities. In an attempt to substantiate this, they experimented with rabbit and dog embryos, in which the blood-supply was reduced before delivery, and alveolar collapse of the lungs was achieved in some of these animals, though no hyaline membrane was seen.

The amount of blood transferred between baby and placenta at the moment of delivery has been a matter for argument. GUNTHER [13] has shown that if the umbilical cord is left untied when the baby is delivered, the baby's blood-volume is significantly higher. (The amount of blood involved may be over 40% of the infant's total blood-volume.) JÄYKKÄ [14] put forward the view that the pulmonary capillaries are erectile and help in the initial expansion of the alveoli when fully distended with blood. The work of BONHAM CARTER [15] also suggests that a high cardiac output is beneficial at the time of onset of extra-uterine respiration. There is thus some evidence that a low blood-volume, with consequently diminished cardiac output, has an unfavourable influence on lung expansion. Furthermore, interference with normal respiratory activity would result in a slowly developing anoxia which in turn would lead to reopening the ductus arteriosus.[16–18] In MAHAFFEY and ROSSDALE's affected foals a widely patent ductus arteriosus was noted at necropsy. While alterations in pulmonary hæmodynamics may partly explain the lack of full pulmonary expansion, they are probably not the only factors in the development of the complete syndrome.

One feature of hyaline-membrane formation in the human infant which was apparently not noted among the foals is desquamation and hyalinisation of the bronchiolar epithelium.[19 20] This change is by no means always

7. Williams, H. M., Diamond, H. D., Craver, L. F. *Cancer*, 1958, **11**, 76.
8. Hare, H. F., Dahle, B. M., Trump, J. G. *Ann. N.Y. Acad. Sci.* 1958, **73**, 363.
9. Farber, S. *ibid.* p. 372.
10. Wilkinson, J. F. *Proc. R. Soc. Med.* 1955, **48**, 365.
11. Bound, J., Butler, N. R., Spector, W. G. *Brit. med. J.* 1956, ii, 1191.
12. *Lancet*, 1958, ii, 945.
13. Gunther, M. *ibid.* 1957, i, 1277.
14. Jäykkä, S. *Acta pædiat., Stockh.* 1957, **46**, suppl. 112.
15. Bonham Carter, R. E. *Lancet*, 1957, i, 1292.
16. Barcroft, J. Researches on Prenatal Life. Oxford, 1946.
17. Lind, J. M. & R. Pediatric Research Conference, Ohio; p. 27. 1955.
18. Hultgren, H. N. *ibid.* 1955, p. 53.
19. Tregillus, J. *J. Obstet. Gynæc. Brit. Emp.* 1951, **58**, 406.
20. Anderson, G. S. *Lancet*, 1958, ii, 1175.

found in the human, and in fact is rather commoner in the extremely immature baby of 1000 g. birthweight or less. The hyalinised epithelium in these infants seems to merge into the membrane proper and there is no sharp demarcation between the two. The significance of this change is not yet known, but the association with gross immaturity suggests that it is a response to some morbid process by very imperfectly developed epithelium and probably does not as a rule play a major part in the development of hyaline membrane.

The atelectatic component of the hyaline-membrane syndrome has also received attention from a different aspect.[21 22] AVERY and MEAD [23] have studied the surface tension exerted by lung extracts from normal infants (mature and premature), adults, and infants dying from hyaline membrane in the lungs. They found that the lowest tension exerted in infants of over 1100–1200 g. birthweight is of the order of 20–30 dynes per cm. In more mature babies and in adults the lowest tensions are under 20 dynes and usually 5–7 dynes. The pattern in 9 cases of hyaline-membrane formation was similar to the pattern in infants of under 1200 g. birthweight, although their weight range was between 1200 and 3500 g. AVERY and MEAD believe that a low surface tension at a period when the lungs are being deflated allows alveoli to remain open if the lung volume is poor: this reduces the tendency of the air-spaces to collapse. If the lung has a high surface tension during expiration, many air spaces will be forced to collapse. They postulate a substance—possibly a protein—which is present in extracts of normal lungs and allows a low surface tension to develop in the air-spaces. This material is, they think, absent in infants showing hyaline-membrane formation. This explanation is plausible because it provides a possible reason for the frequency of the condition among premature babies; but further work is required to elucidate the nature of the hypothetical substance.

Recently an entirely fresh approach has been made to the problem by LIEBERMAN.[24] Examining the lungs of 8 infants dying with atelectasis and hyaline membrane, he found them all deficient in tissue fibrinolytic activity. Such activity, however, was present in their bladder, kidneys, pituitary, and thyroid, and in the meconium of 3 cases. The lungs of some animals were likewise examined for such activity, and it was found in rats and mice though not in guineapigs and rabbits. Of the lungs of 41 other fœtuses, and in infants weighing from 10 g. to 3400 g. at birth, 31 showed activity and 10 showed no activity: in 2 other cases only a trace of activity was noted.

LIEBERMAN suggests that a predisposing factor in hyaline-membrane formation is absence of fibrinolytic activity in the affected infant's lung. This is an attractive hypothesis, since a large part of the membrane is said to be composed of fibrin.[25 26] He holds that the defect, which might represent some genetic aberration, is concerned with plasminogen activation, due to either an abnormal inhibition or lack of tissue activation. This deficiency in lung activity is not to be regarded as the sole factor responsible for the development of a membrane. There is, however, another possible explanation of LIEBERMAN's findings. Activity may be low or absent in these infants' lungs, not because of a genetically determined lack of production but because the supply has been exhausted by the disease process itself. It is surely significant that in 2 other cases where lack of activity was demonstrated the infants died from bronchopneumonia. A fibrinous exudate is a characteristic of this condition, and again the supply may have been exhausted. It may be conceded that hyaline membrane is easily induced in guineapig or rabbit where lungs seem to lack fibrinolytic activity. It is equally easily induced in the mouse, whose lungs do often contain an active material. The resistance of the rat lung to membrane formation in oxygen poisoning is probably more apparent than real: these animals usually die, from a massive pulmonary œdema and hydrothorax, before a membrane has time to develop, and this may not necessarily reflect deficient fibrinolytic activity in the lung.

These recent reports indicate the need for more information on both aspects of this condition. We require more details of the mechanism initiating and maintaining normal expansion of the lung. If the actual structure of the hyaline membrane in the neonatal lung is mainly fibrin, further study of possible modes of formation and destruction of this substance should yield valuable results.

21. Pattle, R. E. *Proc. roy. Soc. B*, 1958, **148**, 217.
22. Pattle, R. E. *Nature, Lond.* 1958, **175**, 1125.
23. Avery, M. E., Mead, J. *A.M.A. J. Dis. Child.* 1959, **97**, 517.
24. Lieberman, J. *New Engl. J. Med.* 1959, **260**, 619.
25. Gitlin, D., Craig, J. M. *Pediatrics*, 1956, **17**, 64.
26. van Breemen, V. L., Neustein, H. B., Bruns, P. D. *Amer. J. Path.* 1957, **33**, 769.

Annotations

PRINTING OF THE LANCET

OWING to a dispute in the printing trade, this issue of *The Lancet* may be distributed late. We regret the inconvenience to readers.

INFORMATION ABOUT NEW DRUGS

THE Hinchliffe Committee considered two ways of achieving good (which is also economical) prescribing.[1] The first—limiting the range of drugs to be prescribed—it regarded as too objectionable. The second way was to provide information on drugs and to improve training and education: " the main difficulty is the dearth of impartial information ". The committee proposed that an independent publication giving up-to-date information about new drugs should be distributed to all doctors in the Health Service. This publication, it suggested, should be financed, but not controlled, by the Ministry of Health—a method that would necessitate great care in making its independence obvious, since the Ministry is interested in reducing prescribing costs.

While this plan was being discussed in committee here, the Americans were acting. Since January a fortnightly Medical Letter on Drugs and Therapeutics has been published by a non-profit-making organisation named

1. Final Report of the Committee on Prescribing Costs. H.M. Stationery Office. 1959. See *Lancet*, May 16, 1959, p. 1027.

Drug and Therapeutic Information Incorporated.[2] With the aid of a panel of distinguished medical advisers the evidence for and against a drug is stated and evaluated. Where the evidence is deemed to be clear, the reader is not left wondering whether the advisory panel believes the drug to be an advance or not. Where the evidence is insufficient, then this is stated and a further report is promised. The Medical Letter has so far expressed opinions on the newer steroids (nothing to choose between them); buffered tetracycline (not a useful advance); meprobamate (little reason to prescribe it in preference to phenobarbitone); chlorpropamide, a new oral antidiabetic agent (the published reports and advertisements do not fully reflect the toxic properties, and a fuller review is being completed); erythromycin propionate (a valuable introduction); and many other preparations. When considering claims of efficacy which are superficially convincing but which yet leave a doubt in his mind, the doctor can now turn to the opinion of experienced people who are not influenced by commercial considerations and who have had time to weigh the evidence. The value of the Medical Letter will depend on its providing up-to-date and reliable opinions, and so far it seems to be succeeding. Good drug firms should welcome this development, for in the long run dissemination of reliable information on their products can only benefit them.

Unfortunately the Medical Letter costs $12.50 a year, and probably not many British doctors will feel inclined to pay individually for a service which, it can be argued, should be supplied free by the State—for it is the State which has the prime interest in inducing them to prescribe economically, though such prescribing is in the patients' interest too. There seems to be real need for a similar publication prepared at first hand in this country, financed by the Ministry but (as the Hinchliffe Committee insisted) run " by the medical profession for the profession ". The American example should encourage the Ministry to seek early action.

RECTAL BIOPSY IN HIRSCHSPRUNG'S DISEASE

In cases of Hirschsprung's disease routine methods of diagnosis often fail to establish the diagnosis; but Swenson et al.[3] have shown that rectal biopsy (which has already proved of value in other disorders [4]) may be a useful aid and may even be the sole means of establishing the diagnosis in infants and in some older children with atypical histories and non-specific X-ray findings.

The patient is prepared for the biopsy by irrigation of the rectum to remove all fæcal material. A general anæsthetic is given to prevent pain and allow the anal sphincter to be widely dilated. A site for the biopsy is chosen on the lateral wall 2–3 cm. above the mucocutaneous junction; the mucosa is incised for 2 cm. and by blunt dissection separated from the muscular layer. A triangular piece of muscular wall, 5 × 10 mm., is removed, care being taken that both circular and longitudinal layers are included in the biopsy material. The defect in the rectal wall is closed by interrupted sutures.

The pathologist may have to examine several sections in order to decide whether ganglion cells are present. Swenson et al. say that in 100 consecutive biopsies in patients considered possibly to have Hirschsprung's disease a positive diagnosis was made in 38. All 38 were operated on, and all the operation specimens showed the typical lesion of Hirschsprung's disease.

2. 136, East 57th Street, New York, N.Y. $12.50 a year ($6 for residents, internes, and students).
3. Swenson, O., Fisher, J. H., Gherardi, G. J. *Surgery*, 1959, **45**, 690.
4. See *Lancet*, 1957, i, 774.

THE EPIDEMIC IN AUSTRALIA

The epidemic of influenza-like diseases now affecting Australia has many confusing and contradictory features, both clinical and virological. A number of epidemic illnesses have appeared since March of this year, and while many of them are clearly attributable to Asian type-A virus, many more may well be unassociated with it.

In Western Australia three clinical syndromes have been noted, often affecting the same patient successively, and virus studies have shown three infective agents—Asian type A, influenza B, and an adenovirus—but their relative incidence among the affected population has not yet been determined. 18 deaths due to secondary staphylococcal pneumonia have been recorded. Among nurses suffering from influenza, *Hæmophilus influenzæ* has been repeatedly isolated from throat swabs and sputum. In South Australia, the epidemic has been widespread with an equally confusing clinical picture. Apart from an illness with typical symptoms of influenza, there have been two other syndromes. In one, symptoms have involved the gastrointestinal tract, with central abdominal colic, diarrhœa, fever, and malaise (the so-called " gastric flu "). This condition has spread in epidemic fashion and been highly infective within families. It has been suggested that an Echo virus may be responsible, but evidence of this has not yet been produced. The second illness usually begins with conjunctivitis, often unilateral, and the palpebral conjunctivæ are often affected to the exclusion of the globe. Though rapidly becoming purulent, the discharge contains no specific organisms. The condition is unaffected by topical antibiotics and is often accompanied by preauricular adenitis and the symptoms of an upper respiratory infection. There is some evidence to support the view that this illness is caused by an adenovirus, but the type has not yet been identified. So far, there have been 14 deaths in South Australia associated with the epidemic, but not all were clearly related to infection with influenza virus. Rather more deaths have been recorded in the sixth and seventh decades than in the 1957 outbreak. Material examined from 3 fatal cases of staphylococcal pneumonia has contained two strains belonging to phage-type 80/81 and one to group III (7/47D+). All have been resistant to penicillin but sensitive to other antibiotics.

Victoria and New South Wales have suffered severely, and it is estimated that in the first two months of the outbreak in Sydney 23 deaths were attributable to influenza and its complications. Isolations both in Melbourne and in Sydney have shown Asian type-A virus. In one children's hospital in Victoria, however, admissions did not increase and there was no rise in the incidence of laryngotracheitis, as there was in the 1957 epidemic. Many of the staff of this hospital suffered an influenza-like disease, and virus studies have revealed two types of Echo virus, as yet unidentified. Throughout Australia, native populations have been severely attacked. Millingimbi Mission, near Darwin, reports that almost the entire colony of 400 has been affected. Thousands of natives in Arnhem Land and on Croker, Bathurst, and Elcho Islands have also had influenza, and a recent outbreak amongst aborigines at the Coober Peedy opal mining area has brought 3 deaths.

Influenza vaccine has been made available by the Commonwealth Serum Laboratories, and the National Health and Medical Research Council has been consider-

ing a proposal for nation-wide influenza inoculation. Vaccination programmes so far have mainly covered the staffs of hospitals and large industrial concerns, and it is too early to assess the degree of protection conferred by the vaccine. Although influenza is a notifiable disease in many States, it is doubtful whether this regulation results in more than a fraction of the total number of cases being placed on record. And this, together with the confusion introduced by other viruses, makes it almost impossible at present to assess the epidemic.

AN INTELLIGENT FRIEND

TODAY the golden eagle is to be found in only one small part of the globe. Tomorrow the general practitioner, another increasingly rare bird, may well be found only in Britain. In progressive countries, to the right of us and to the left of us, he is rapidly being replaced, according to political taste, by specialists or by policlinics. So far British family doctors have been reluctant to lose sight of the patient among his syndromes and systems. Their insistence on the ideals of "continuing responsibility" and "prevention and treatment" (to borrow the words of Dr. John Hunt, the honorary secretary of their own young and robust college) is beginning to have effect. Consultants, administrators, and laymen are slowly learning that though the patient may no longer want a father figure, or a dispenser of placebos, he still badly needs an expert and intelligent friend with first-hand knowledge of his background and medical history.

There thus appears to be an assured place for the family doctor in contemporary medicine in this country; but if he is to fill it adequately, some changes will have to be made in his way of practice. Conservative and libertarian by nature, he often is slow to initiate change and sometimes grudging in accepting it; and in a pamphlet on the Future of the Family Doctor, Dr. Bruce Cardew [1] suggests that changes will have to be planned by the Ministry of Health. In the first ten years of the National Health Service, general practice, he suggests, has not been cherished with the same administrative fervour as, say, the hospital service. The general medical services cost the country over £70 million a year. To administer them there is available a quarter of the time of an undersecretary, half of the time of an assistant secretary, and the whole time of a principal secretary. In Dr. Cardew's view this degree of understaffing makes intelligent planning almost impossible.

Furthermore he points out that changes can only be introduced at "grave initial inconvenience to established doctors". It would seem, therefore, only reasonable to offer the doctors incentives to adopt these beneficial inconveniences. The most obvious, though not the only, incentive is money; yet the present methods of payment, Dr. Cardew suggests, sometimes seem to be designed to discourage doctors from improving their surgeries, employing ancillary help, or buying new equipment, and to encourage competition for patients and overlong lists. He also regards the present arrangement for group-practice loans as inadequate. Like Collings,[2] he suggests that to make any real change in the organisation of practice the Government must provide adequate and realistic subsidies. Cardew proposes that the Government should set up a trust fund to build or convert premises which the trustees could lease to doctors. In this way he believes that 500 doctors could be accommodated each year at an annual cost of £1 million.

A few weeks ago we reaffirmed [3] our belief in the renaissance of general practice. This critical pamphlet is Dr. Cardew's affirmation of faith. It is more sincere and may well prove more effective than many less captious tributes.

MEDICAL SCHOOL OF CAMBRIDGE

Cambridge has now had a school of clinical research and postgraduate teaching for 12 years. The question whether it should also have an undergraduate teaching school has often been asked, and has now finally been answered by the decision not to build one. The university authorities say that "the proper course for the university is to concentrate its resources on the development of the thriving postgraduate medical school, and not to dissipate resources by setting up a pre-graduate medical school".[4]

The new buildings for the postgraduate school will be put on part of the 44-acre site for the new Addenbrooke's Hospital, which has frontages on both Long Road and Hills Road. Designs for the department of radiotherapeutics have already been commissioned, and it is hoped that building will be completed by the end of next year. The needs of the department are urgent because its present buildings are to be taken over by the department of biochemistry by the end of 1960. The move will be greatly helped by the gift of £60,000 from the Wellcome Trust towards the cost of the new buildings.

"NEW" DRUGS IN PSYCHIATRY

AN international study group of the World Health Organisation has reviewed [5] the present position of the ataractic and hallucinogenic drugs, such as mescaline and chlorpromazine. Despite more than a fair share of growing pains, some excellent work has been done and, now that the need for meticulous attention to detail is more widely recognised, much more progress may be expected in the next few years from the many laboratories now involved. The main advances have been in the basic pharmacology and biochemistry of known active agents, such as L.S.D. 25, serotonin, and chlorpromazine, and in the clinical development of empirical therapeutic drugs. Unhappily, our knowledge of the basic biochemical faults that probably lie behind the major psychoses has hardly advanced at all, despite the considerable efforts directed in this direction. The W.H.O. study group is rightly rather gloomy about this lack of progress, and they trace it to some of its causes—the very short time since this work began on an effective scale, lack of basic knowledge, lack of adequate controls, failure to realise the complexity of the ancillary factors, and over-eagerness to stake claims to priority in a field laden with potential rewards.

The report opens with a penetrating and liberal assessment of why these drugs remained for so long entirely unknown, except among a few specialists. The subjective and bizarre phenomena induced by mescaline and their close similarity to some varieties of religious experience made these drugs rather an embarrassment to these psychiatrists who were for so long the only professional

1. Obtainable from the Fabian Society, 11, Dartmouth Street, London, S.W.1. 1959. Pp. 29. 2s. 6d. (postage 2d.)
2. Collings, J. S. *Lancet*, 1953, ii, 875.
3. *ibid.* May 16, 1959, p. 1029.
4. *Cambridge University Reporter*, May 27, 1959, p. 1477.
5. Ataractic and Hallucinogenic Drugs in Psychiatry. *Wld Hlth Org. tech. Rep. Ser.* 1958, no. 152. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1. Pp. 72. 3s. 6d.

group in close contact with them. During the first half of this century only a handful of workers, such as Klüver and Stockings, had any understanding of their real importance to psychiatry. The group select two events as mainly responsible for the sudden change in the early 1950s from neglect to the blaze of popularity these drugs now enjoy in research institutions all over the world: the discovery that minute doses of L.S.D. 25 can cause profound mental disturbances in man; and the discovery of the therapeutic efficacy of the phenothiazines and the rauwolfia alkaloids in psychosis. But these were only minor (though important) factors and they were not really responsible for the change. The hallucinogenic properties of L.S.D. 25 were first reported in 1943, and the group place the change about 1952. Moreover, the mere fact that a very small dose of a drug can cause mental disturbances is not very significant; for, though the phenothiazines can alleviate psychotic symptoms, so could insulin coma before them. The two observations which, when conjoined, were mainly responsible for the growth of this branch of psychopharmacology were (1) the realisation that there are some close similarities between the effects of the hallucinogenic drugs and some symptoms of schizophrenia, and (2) the fact that some of these drugs (such as mescaline and L.S.D. 25) are chemical relatives of compounds known to be present in the brain (such as adrenaline and serotonin). These two facts *together* gave a clue to the kind of biochemical fault that *might* be responsible for psychosis and replaced a complete absence of ideas, beyond vague notions that amines, indoles, or "toxin *x*" were responsible.

These new specific hypotheses of the ætiology of schizophrenia have not received any noteworthy confirmation, but that is not important compared with the volume of work in basic neuropharmacology and allied sciences to which they have lent impetus. What is now required is much more basic work on such aspects as the neurochemical action of these drugs and the neurochemical mechanisms underlying emotions and other higher mental functions, and an examination of any differences in these mechanisms in schizophrenics and non-schizophrenics, with close attention to the many confusing factors already revealed (such as diet, age, non-specific stress, emotion, placebo effects, suggestion, and auto-suggestion). Earlier work demonstrated the importance of these influences, but failure to take them into account made it impossible to accept any of the claims that have been made, except some very recent findings which were adequately controlled (for example, results at the National Institutes of Mental Health and the Worcester Foundation, and Rodknight's investigations at the Maudsley Hospital). New hypotheses are also needed, and current research suggests a shift of attention towards histamine and such basic mechanisms as transmethylation enzymes; and the idea of sensitivity or disordered response towards a metabolite normally produced in stress is also being considered. Early efforts should not be discredited, however, since their failures have demonstrated the great complexity of the subject and have opened the way to newer and more definitive inquiries.

The W.H.O. report emphasises two points fundamental to such investigations: (1) the catechol amines and indoles known to be present in the brain may merely be members of whole families of closely related compounds in these classes whose interactions in the brain may underlie the control of affective behaviour; and (2) the possible dichotomy between intracerebral metabolism of certain compounds and their fate outside the brain. (It is this dichotomy that keeps alive theories of the ætiology of schizophrenia based on simple faults in adrenaline and serotonin metabolism—for all the tests that have proved negative have involved extracerebral loci. The endogenous metabolism of such compounds may be quite different inside the brain, and these alternative paths may still be affected in schizophrenia.) Direct work in man is thus rather difficult, but modern techniques, such as systematic loading experiments and the use of radioactive tracers, are now in use in a number of centres.

SUPPLY OF CHEMICAL PATHOLOGISTS

KNOWLEDGE of the biochemical mechanisms of disease has increased strikingly in the past few years, and the pace of development shows no slackening. The demand for consultants in chemical pathology has outstripped the supply, and a vicious circle has arisen: some boards have been reluctant to advertise posts for chemical pathologists because suitable candidates are so scarce, and trainee pathologists have been reluctant to specialise in this subject because so few vacancies are advertised. The need cannot be met by the appointment of non-medical biochemists who have already obtained a degree in chemistry or biochemistry: control of the routine analytical procedures of a laboratory carried out by technicians, and sometimes by biochemists, is a duty which could no doubt be equally well carried out by the non-medical scientist; but a more difficult and in many ways more important task of the chemical pathologist is to advise his clinical colleagues as to the most useful lines of investigation and on the interpretation of the results, not only for diagnosis but also for the control of treatment; many of the disorders where his help may be sought are ill-defined clinically, and for his opinion to be useful he must have considerable medical knowledge.

Some of the present chemical pathologists have trained as chemists and gone on subsequently to obtain a medical qualification, and this training is probably the ideal one; but the number was always small and the training very long, and, with the added time of national service, the supply by this route has all but dried up.

The Association of Clinical Pathologists, which has been considering this problem for some time, indicated its urgent importance to the Ministry of Health. The Ministry has now created four special registrar posts, one of which is advertised in this issue, and it is proposed to continue to appoint four more registrars each year until the position is stabilised.

These posts will be held by trainees who after their usual house appointments have had at least two years' training in general pathology (usually a year as senior house-officer and the first year of a registrar appointment), but they differ from ordinary registrar posts in that the trainee will spend only about half his time in the hospital laboratory and the other half in the formal study of chemistry and biochemistry at a university or polytechnic. It is not expected that the registrars will necessarily work for any special degree or diploma in chemistry. After this period of registrar training the trainees will, it is hoped, obtain appointments as senior registrars in laboratories where most of their time will be devoted to chemical pathology. Under this scheme, about five years hence, additional trained chemical pathologists will become available at the rate of four a year.

Points of View

THE PROPER PROCEDURE

T. G. LOWDEN
B.M. Oxon., F.R.C.S.
CONSULTANT SURGEON, SUNDERLAND GROUP OF HOSPITALS

CASE 1.—A patient with a sudden cerebral thrombosis fell in consequence of it and split his scalp. The family doctor arranged for his admission to Hospital A, and was advised that as this hospital had no casualty department, the ambulance should call at Hospital B on the way and have the scalp sutured. The house-surgeon at Hospital B came down to the casualty department, sutured the scalp as requested, and sent the patient on. Three hours after admission to Hospital A the patient died of his cerebral thrombosis. The consultant concerned at Hospital A reprimanded the house-surgeon of Hospital B, maintaining that the proper procedure if the patient was so seriously ill was to admit the case to Hospital B, and countermand the arrangements already made for admission to the original hospital.

CASE 2.—A man had a gastrectomy by Mr. X in 1953. In 1954 he perforated an anastomotic ulcer and was operated upon as an emergency by Mr. Y. He was sent to the casualty department in 1955 on Mr. Z's emergency day with another perforation. Mr. X's house-surgeon declined responsibility on the grounds that Mr. Y had operated more recently. Mr. Y's house-surgeon responded similarly because it was not his firm's emergency rota, and Mr. Z's emergency beds were in another hospital. The proper procedure therefore appeared to be to put the case into another ambulance (the first had disappeared) and transfer him to Mr. Z's hospital. This the casualty officer stoutly refused to do. The case was admitted to a supernumerary bed in Mr. Y's ward, and Mr. Z operated upon it in Mr. Y's absence.

CASE 3.—An accident case was brought into the casualty department. He had a history of unconsciousness, abdominal guarding, and pain in the back. The casualty officer admitted him to the general surgical ward but arranged an X-ray of the skull on the way. By the time the patient was in bed the X-ray plate arrived and showed a fissured fracture lying across the posterior branch of the middle meningeal artery. The consultant general surgeon came to see the patient and suspected damage to the spleen, but also detected deformity in the lumbosacral region; and a further X-ray showed a fracture-dislocation of the spine. The consultant orthopædic surgeon, the consultant general surgeon, and the casualty officer agreed that any decision might prove to be the wrong one. If intra-abdominal hæmorrhage developed, he was in the right place. If extradural hæmorrhage developed, he should be at the neurosurgical centre (some miles away), and if neither developed he should be in the orthopædic theatre (again, in another hospital) for open reduction of his vertebral injury. Two senior consultants and the casualty officer sat late into the night, and failed to decide the proper procedure for this case. The clinical course resolved the dilemma, and the patient was transferred on the following day to the orthopædic centre, where the orthopædic surgeon successfully reduced the fractured spine.

Although the casualty officer, from the nature of his appointment, is that junior officer most often and most immediately involved in these problems of disposal, other residents and subordinate doctors find themselves in similar difficulties.

CASE 4.—A patient was sent into hospital with a diagnosis of perforated peptic ulcer. The resident surgical officer saw the patient in the receiving-room and considered that the case might be more reasonably diagnosed as coronary thrombosis. He rang up the surgeon who advised that if there was any doubt the patient should be admitted to the surgical side. The surgeon came in soon after the patient reached the ward and confirmed the R.S.O.'s diagnosis. He told him to arrange transfer to the medical side on the following morning, if the patient was fit to be moved, but not to disturb him immediately as he was settling down comfortably. Four days later the R.S.O. was reprimanded for failing to arrange the transfer. The R.S.O. had in fact asked for transfer, but the consultant physician refused to accept the case until the proper procedure had been carried out. The proper procedure was for the consultant surgeon to send the consultant physician a consultation form requesting him to see the case and consider transfer. The consultant surgeon had omitted to do this, so the R.S.O.—and the patient—were the sufferers.

SOME LESSONS

One could report other cases like these. From discussions in casualty departments with junior medical officers, and with consultants in many parts of the country, I think that similar problems exist in every part and at every level of the hospital service. All these casualty officers, senior residents, and consultants have local customs, and many have written instructions to justify their decisions. The " proper procedure " is the result of long experience in organising the relations between different departments and different hospitals. In many cases it has been reduced to black and white by management committees after much deliberation, and with full awareness of the difficulty of integrating the different parts of the system. Yet, the present situation of admission of urgent cases to hospital, the decision on which part of the hospital they should go to, and the transfer of urgent cases from the receiving-room of one hospital to the ward of another (though working fairly satisfactorily in the majority of cases) leave loopholes through which slip a considerable number of cases such as the four I have described.

The professional tradition that, once a consultant has accepted clinical responsibility for a case, it should be referred to him when there are subsequent relapses or complications is having to give way before the practical considerations of a nation-wide hospital service. No consultant can hold himself available at all times to attend to emergencies in the hospital, nor does the service expect him to. Nor do consultants, as a rule, attend to the day-to-day details of admission of such cases to their wards. Considerable responsibility for the disposal of cases rests with the resident staff, and they are expected to pick up for themselves the principles of a system which can very often be interpreted in several different ways.

A generation ago general practitioners were being exhorted to send their emergency cases into hospital in the early stages of the disease. Surgeons, for instance, protested that they could not be expected to cure cases of appendicitis if they were a week old when they arrived, with pus under the diaphragm. Nowadays practitioners cannot be blamed, therefore, for sending for admission many cases which prove, after a day or two's observation, to need little treatment and no surgical intervention. Present-day surgeons are getting what their predecessors asked for. They are finding their wards embarrassed by emergency cases admitted for observation, and cannot admit their waiting cases because the beds are filled by " acutes ". Medical emergencies are acquiring a somewhat similar disadvantage because so many of them are admitted for social rather than medical reasons, and patients sent in with a rather tenuous diagnosis cannot be sent home again because their relatives are unenthusiastic about their return.

For these (and doubtless many other) reasons, residents may conclude that they will best win the approval of their chief if they are successful in " wishing " upon other departments as many emergencies as they can, and I suspect that such a conclusion is not altogether unjustified. The development of litigious skill in interpreting the " proper procedure " favourably to their own firm is an early part of their postgraduate experience.

Few residents will now accept responsibility for returning patients from the receiving-room to their general practitioner, even when they feel that there is nothing seriously the matter. On too many occasions have mistakes brought residents into serious legal trouble. " Admission for observation " gives the same sort of medicolegal protection to the resident as an " X-ray to eliminate fracture " (and we know how many clinically unnecessary X-rays are taken). In a system where one doctor admits to a second who accepts on behalf of a third, stresses and strains are set up which are of no profit to any of the doctors concerned, nor to the patient.

SCATTERED RESOURCES

Each of the cases quoted shows how interpretation of the " proper procedure " might fail to serve the interest of the patient. In case 1 I have no doubt it would have been better for the dying man to be held at Hospital B (if Hospital A was in fact unable to put stitches into a scalp) whether Hospital B was the " proper " hospital for him or not. I hesitate, however, to expect a house-surgeon to countermand all existing arrangements with one department and insist upon another one accepting an unexpected case, on a few minutes' clinical assessment. Hospitals cannot elaborate a system for their doctors to obey and then blame them for failure to defy it. Yet a hospital officer did, in fact, defy the " proper procedure " in case 2, with excellent results. Messrs. X, Y, and Z conferred together upon who was to accept further responsibility for this case, but the immediate emergency was resolved by a prompt decision to cut red tape, and the patient's interests were adequately served.

The number of patients with established claims on many departments is increasing steadily, and apart from a more-or-less dignified game of " slippery Ann " I can think of no way of dealing with them. An earnest attempt on the part of three surgeons, two of them with long experience, failed to disentangle the clinical dilemmas in case 3. They determined, in fact, to resolve one part of the problem by carrying out craniotomy themselves, if it became imperative, because it was clearly unwise to move a patient whose spleen may have been ruptured to the regional head-injury centre. They were still faced with transfer of the patient to a place with special facilities for operation on the spine. I am not aware, again, of any " proper procedure " for cases of this type with multiple injuries.

Case 4 needs little further comment. A lofty disdain for the proper procedure on the part of one consultant, and a rigid insistence upon it on the part of another, resulted (as often happens) in the frustration of an innocent subordinate, delay (albeit harmless) for an unfortunate patient, and the waste of four bed-days from the hospital's economy.

In the first three of these cases there is one common factor. Many areas acquired a number of hospitals with the start of the Health Service, and have, on the one hand, concentrated special centres in one of these and, on the other, " upgraded " some of them to deal with acute general medicine and surgery. Sharing out the various " zones of influence " among individual consultants has resulted in different hospitals dealing with similar emergencies on different days, in different types of emergency having to be moved in different directions on the same day—and in patients with multiple conditions (particularly multiple injuries) depending on skilled and early assessment of the relative urgency of their several lesions before they can be properly directed at all. Sometimes (as in case 3) it appears to be quite impossible to do this.

The scattered distribution of the emergency facilities increases the probability of a patient arriving at the wrong hospital, and the necessity for transferring patients from one hospital to another. It puts a heavy burden on the general practitioner, and a heavier one still on ambulance and other public services which may have to decide the disposal of emergency cases without any medical help. The junior medical staff—and receiving-room staff in particular—are the next to take the strain, and the consultant least of all. Any scheme of instructions on the proper procedure, however comprehensive, is bound to be open to many interpretations. As these cases show, it cannot cover all the eventualities.

In the past few years the peripheral hospitals have become very short of junior hospital officers, and of residents in the intermediate grades. There is much deputising one for another among those that there are, so that they can enjoy some free time, and so that they can sleep. Not only are their numbers inadequate, but they change their appointments once or twice a year. The hospitals are frequently faced with the necessity to train a new staff in the complex arrangements by which the right patient is put into the right bed. Many of the residents themselves are not only imperfectly acquainted with the arrangements, but imperfectly acquainted with the language in which they are made, and have been trained, in their own countries, to a literal and uncritical execution of their instructions. These men and women cannot be expected to use their own discretion in interpreting the instructions, and at the same time be denied the authority to do so.

REMEDIES

This aspect of the hospital service will profit by further examination. A review is needed of the extent to which the facilities for emergency work have been split up amongst the many small hospitals bequeathed to us in 1948, and of how far the various different departments should be gathered together again under one roof. If each area had one hospital—and one hospital only—to which all types of medical, surgical, and accident case should be sent, many of these difficulties would disappear. Many others would be solved if decisions could be made on such problems as the disposal of the " return " case, the case with doubtful diagnosis, and the case with a claim on more than one clinical firm or more than one specialty. More, again, could be reduced, if not solved, by putting beds at the disposal of the casualty department itself, where patients could be accommodated and treated while decisions on the " proper procedure " were made by the various authorities involved. Patients tend to lie in casualty departments waiting for these decisions, and accommodation should be provided while they wait—accommodation which approxi-

mates to a ward bed rather than an odd corner of a department busy with other and mainly ambulant cases.

A conference was held in Newcastle upon Tyne last year, to which were invited various people interested in the work of casualty departments. It included clinicians, administrators, and architects, registrars, senior casualty officers, and consultants—neurosurgeons, plastic surgeons, general and orthopædic surgeons, and physicians. Some represented the teaching hospitals and cities, and some the remotest parts of the periphery. I heard many of them advocate the establishment in their own hospitals of a casualty ward—beds whose proper function would be, not to be occupied (*pace* the administrators), but to be empty and ready. Of all these people, seeing the problem from the practical point of view (which is the patient's point of view), none spoke against it.

Public Health

SPUTUM EXAMINATION AND THE INVESTIGATION OF "CHRONIC BRONCHITIS"

P. C. ELMES
B.M. Oxon., M.D. Western Reserve, M.R.C.P.
LATE SENIOR REGISTRAR, HAMMERSMITH HOSPITAL, LONDON, W.12

A. A. C. DUTTON
B.M. Oxon.
ASSISTANT LECTURER IN BACTERIOLOGY

C. M. FLETCHER
C.B.E., M.A., M.D. Cantab., F.R.C.P.
PHYSICIAN TO THE HOSPITAL

From the Departments of Medicine and Bacteriology, Postgraduate Medical School of London, W.12

EXPECTORATION in public, which used to be a common habit, has now nearly disappeared in London. Over the past fifty years propaganda has clothed it with such shame that patients with frequent productive cough dare not leave the house. A recent migrant to London from a less particular society found his habit so embarrassing that he returned home without seeking any cure.

This apparent disappearance of expectoration might be taken to indicate a falling off in the incidence or severity of diseases associated with productive cough. The observer wishing to discover the truth is not only hampered by the habit being confined to the privacy of the home but if he depends on verbal evidence alone he may be faced by a reluctance to admit the entire truth. Furthermore the lack of studies of expectoration may arise from the unwillingness of field workers to undertake such distasteful work.

In a survey of respiratory symptoms the main object was to study the reliability of a questionnaire by measuring its repeatability (Fairbairn and Wood 1959). Its validity was to be assessed by simple respiratory-function tests, and by the inspection of sickness-absence records (Fletcher, Elmes, Fairbairn, and Wood 1959). Although the only way to check the validity of answers concerning expectoration directly is to examine the subject's sputum (Fletcher et al. 1959), it was suggested that to attempt such an examination would be to forfeit the cooperation of the population. Not until the questionnaire had been completed and a good rapport established between the investigators and the subjects, did we dare (at the insistence of Dr. Philip Hugh-Jones) to ask for specimens of sputum. The response from the men on this first occasion was so profuse that we were unable to investigate the specimens completely, and we were encouraged to carry out a detailed study of further specimens collected from both the men and the women in March and August.

This report is concerned with the remarkable response to our request for specimens and the value of this technique for investigating the prevalence and nature of chronic respiratory disease.

Methods

This investigation was confined to the 144 postmen of the London East Central District Office and 144 women "sorters" employed in clerical duties by the Post Office Savings Bank in London who were given the questionnaire on two occasions (Fairbairn et al. 1959). Half of each group were aged 40–49 years, and half 50–59.

Collection of Specimens

A single morning specimen was obtained by issuing sterile universal containers to all the subjects with a letter which thanked them for their cooperation and continued:

"We now want to ask you to help in one more way. It sounds rather inquisitive but it is actually very important. We want to see what sort of phlegm ordinary people cough up in the morning. If you do ever cough up any phlegm could you take this bottle home with you and spit into it *all* the phlegm you cough up during the first hour after you get up out of bed tomorrow. We don't want spittle from your mouth but only phlegm from your chest."

Bottles were to be returned whether full or empty. They were identified by a number only, and the subjects were assured that our findings would be confidential.

Examination of Specimens

Macroscopic.—The volume and appearance were recorded without opening the containers. Assuming that the containers were uniform in shape, the volume of sputum was measured in centimetres up the side of the vessel and converted into millilitres by multiplying by four.

The classification according to appearance gave rise to more difficulty than was expected in spite of using four simple categories:

1. Food and saliva only.
2. Pure mucoid.
3. Mucoid with diffuse pus or with purulent blobs.
4. Pure pus.

Of 166 specimens examined independently by two observers 89 (54%) only were placed in the same category on both occasions. To avoid bias between the sets of specimens the classification of one observer (P. C. E.) was used throughout. This observer reexamined a set of 70 specimens and found 75% repeatability.

Bacteriological.—Methods described previously (Elmes, Fletcher, and Dutton 1957) were used, except that cultures were also put up for *Mycobacterium tuberculosis*.

Cytological.—Carnoy-fixed smears stained with pyronin, methyl-green, and toluidine-blue (Elmes, Knox, and Fletcher 1953) were used to demonstrate the presence of pus cells, Curschmann's spirals, dust cells, eosinophils, and fibrous proteins.

Ventilatory-function Tests

The fast-expiratory volume (B.T.P.S.) (1 second) (F.E.V. 1·0) was used to detect loss of ventilatory function. Those subjects who admitted to no symptoms of respiratory disease were regarded as normal and their readings were used to establish the relation between the F.E.V. 1·0 and the subjects' ages. The results from each subject were then adjusted to a standard age (40 years) before calculating the indirect maximal breathing capacity (M.B.C.).

Results

Macroscopic Findings

To our surprise half the men and a quarter of the women produced sputum (table I). About half the specimens contained pus (table II), and more than a quarter of the men produced more than 2 ml. of sputum in winter (table III). The character of the sputum varied according to age, sex, and season of the year, but not always according to expectation.

TABLE I—NUMBER OF SPECIMENS

Group		No. of subjects available*	Percentage of bottles		
			Containing sputum	Empty	Not returned
Winter	Men 1st specimen	144	49	40	11
	Men 2nd specimen	133	50	39	11
	Women	144	22	78	0
Summer	Men	121	45	53	2
	Women	128	13	82	5

* The groups should all have contained 144 subjects, but by the time the second winter and the summer collections were made, some subjects were not available because they had changed their jobs, or were on sick or annual leave.

Thus more of the older men produced sputum, but the mean volume of each specimen was not significantly greater than that from the younger men (table IV). There was no difference in either respect between the older and the younger women. In summer the men produced significantly smaller specimens of sputum than in winter, although the proportion producing specimens did not fall significantly. Although fewer women produced specimens in the summer the difference is not significant.

The proportion of specimens appearing purulent or mucopurulent showed no significant variation with sex or season (table II).

TABLE II—MACROSCOPIC APPEARANCE OF SPUTUM

Specimen		Number of specimens	Appearance (%)			
			Saliva or food	Mucoid	Mucopurulent	Pus
Men	1st winter ..	70	6	29	64	1
	2nd winter ..	66	7	39	49	5
	Summer ..	54	2	41	54	3
Women	Winter ..	31	7	48	45	0
	Summer ..	17	17	47	30	6

The measurement of sputum volume by our method is less subject to error than the macroscopic appearance, and, to assess the repeatability of sampling, the two winter specimens from the men were compared (table V). Of those who returned an empty bottle the first time, 76% did so on the second occasion. Of those who returned specimens on both occasions, 65% brought up the same quantity and only 4% produced a volume of sputum on the second occasion which differed from the first by more than one arbitrary category of volume. Thus, although a single collection can only provide a rough guide to a single subject's expectoration habits, it does appear to be satisfactory for measuring the frequency and amount of expectoration in a group of the population.

TABLE III—EFFECT OF AGE, SEX, AND SEASON ON VOLUME OF SPECIMENS

Collection	Sex and age in years		Percentage of available population who returned specimens of volume			
			Up to 2·0 ml.	2·0–6·0 ml.	Over 6·0 ml.	All vols.
Winter	Men 1st specimen	40–49	17	18	5	40
		50–59	22	17	18	57
	Women	40–49	14	4	3	21
		50–59	12	8	2	22
Summer	Men	40–49	27	8	3	38
		50–59	27	15	8	50
	Women	40–49	11	3	0	14
		50–59	9	2	2	13

TABLE IV—SIGNIFICANCE OF DIFFERENCES DUE TO AGE AND SEASON

Groups compared	Index of comparison	Test	Probability of difference occurring by chance
Women: winter *v.* summer	No. of specimens	χ^2	0·2 to 0·1
Men: 40–49 *v.* 50–59 ..	No. of specimens	χ^2	0·01 to 0·001
Men: 40–49 *v.* 50–59 ..	Group total sputum volume	t	0·01 to 0·001
Men: 40–49 *v.* 50–59 ..	Volume of specimens	t	0·1 to 0·05
Men: winter *v.* summer	Volume of specimens	χ^2	0·01 to 0·001

Table VI shows the consistency in appearance of the two winter specimens. The apparent individual variation is again high, only 54% producing sputum of the same appearance on both occasions. But again the distribution between categories for the whole group is very similar on the two occasions.

TABLE V—COMPARISON OF BOTH WINTER SPECIMENS BY VOLUME

—		1st specimen				
		Returned empty	Up to 2·0 ml.	2·0–6·0 ml.	Over 6·0 ml.	Total
2nd specimen	Returned empty	**38**	5	2	2	47
	0–2 ml.	8	**13**	5	1	27
	2·0–6 ml.	4	4	**12**	3	23
	Over 6 ml.	0	1	4	**9**	14
	Total	50	23	23	15	111

Bacterial and Microscopic Findings

The bacteriological and microscopic findings were similar to those we have reported in the sputum of outpatients with chronic bronchitis (Elmes et al. 1957). None of the specimens contained more than 5% eosinophils.

Of the organisms usually considered pathogenic to the lower respiratory tract (May 1953), *Hæmophilus influenzæ* and *Streptococcus pneumoniæ* were most frequently cultured in significant numbers (table VII); other pathogens were only occasionally found. The frequency of a heavy growth of both *H. influenzæ* and *Str. pneumoniæ* is remarkably consistent (about 45% and 25% respectively), except for the summer specimen from the women. It is different from the incidence reported using the same methods on outpatients with bronchitis who were still at work in the winter of 1955–56 (Elmes et al. 1957). In that study 63% of the sputum yielded *H. influenzæ*, 13% *Str. pneumoniæ*. It is possible that the prevalence of each infection varies from winter to winter.

TABLE VI—COMPARISON OF BOTH WINTER SPECIMENS BY APPEARANCE

—		1st specimen				
		Saliva or food	Mucoid	Mucopurulent	Pus	Total
2nd specimen	Saliva or food	**0**	1	1	0	2
	Mucoid	1	**7**	11	0	19
	Mucopurulent	1	7	**20**	0	28
	Pus	0	1	1	**1**	3
	Total	2	16	33	1	52

Tubercle bacilli sensitive to streptomycin, isoniazid, and para-aminosalicylic acid were recovered from the sputum

of 1 subject; he was not known to have tuberculosis, but investigation revealed a lesion at the apex of one lung and arrangements were made for him to be treated.

Interrelation of Sputum Findings

The association between a heavy growth of *H. influenzæ* and the presence of pus in the sputum (May 1953, Elmes et al. 1953) is confirmed by our results (table VIII). The relation is not absolute but is highly significant. There was a positive association between a heavy growth of *H. influenzæ* and a heavy growth of *Str. pneumoniæ* (table IX) and no relation could be shown between the

TABLE VII—RESULTS OF BACTERIAL CULTURES

Specimens		Numbers of specimens yielding a growth of					
		H. influenzæ			*Str. pneumoniæ*		
		0 or ±	+	++ or +++	0 or ±	+	++ or +++
Male	Winter (2nd)	34	5	27 (41%)	43	6	17 (26%)
	Summer ..	22	5	25 (48%)	29	10	13 (25%)
Female	Winter ..	16	2	13 (42%)	26	0	5 (16%)
	Summer	11	0	6 (35%)	14	0	2 (12%)

growth of *Str. pneumoniæ* alone and the purulence of the specimens.

There was no relation between the volume of the sputum and its purulence, or between the volume and the growth of bacteria. Significantly more specimens containing spirals and numerous dust cells were found among those appearing mucoid than among those appearing purulent, but there was no association between dust cells and spirals.

Relation between Sputum Findings and Other Objective Data

The two objective tests that were applied to the population at the time of the questionnaire were the measurement of ventilatory function and investigation of official sickness-absence records.

TABLE VIII—RELATION BETWEEN PURULENCE AND BACTERIAL GROWTH

Appearance of sputum	Number of specimens yielding a growth of *H. influenzæ* *			Number of specimens yielding a growth of *Str. pneumoniæ* †		
	+ or less	++ or more	Significance	+ or less	++ or more	Significance
Mucoid	41	16	$\chi^2=9{\cdot}4$ P=0·01 to 0·001	41	9	$\chi^2=0{\cdot}23$ P=0·7 to 0·5
M.P. or P.	27	34		28	8	

M.P. = mucopurulent. P = purulent.
* Specimens yielding ++ or more growth of *Str. pneumoniæ* excluded.
† Specimens yielding ++ or more growth of *H. influenzæ* excluded.

The volume of the sputum specimens was the only characteristic correlating significantly with a reduction in M.B.C. (table X). No relation could be demonstrated between the purulence of the specimens or the presence of pathogenic organisms and loss of ventilatory capacity. The F.E.V. 1·0 expressed as a percentage of the vital capacity (F.E.R.) (Capel and Smart 1958) was used as an index of airway obstruction. No correlation could be demonstrated between a reduction in this ratio and the presence of Curschmann's spirals, nor were spirals found significantly more frequently in specimens from subjects who complained of wheeze (table XI).

TABLE IX—RELATION BETWEEN GROWTHS OF *H. influenzæ* AND *Str. pneumoniæ*

—	—	Number of specimens yielding a growth of *H. influenzæ*		
		+ or less	++ or more	Significance
Number of specimens yielding a growth of *Str. pneumoniæ*	+ or less	80	49	$\chi^2=4{\cdot}79$ P=0·05 to 0·02
	++ or more	14	20	

TABLE X—RELATION BETWEEN SPUTUM VOLUME AND VENTILATORY CAPACITY IN MALES
(First winter sputum specimen only)

—		Volume			
		Empty	Up to 2·0 ml.	2·0–6·0 ml.	Over 6·0 ml.
Winter	No.	50	28	25	15
	Indirect M.B.C.	114	122	109	82
Summer	No.	63	33	14	7
	Indirect M.B.C.	113	118	98	69

Between "empty" and "over 6·0 ml." in winter t=4·34, P=0·001.
Indirect "M.B.C." was calculated from the fast expiratory volume (1·0) (reduced to B.T.P.S. and corrected for age) by multiplying by 35.

An apparent anomaly in the relation between sputum volume and reduction in M.B.C. is revealed in table X. The subjects who returned empty containers had a lower mean M.B.C. than those who returned a small quantity of sputum. The difference is not statistically significant but it was found in both the winter and the summer specimens. This can be explained in two ways: either, the "returned empty" group contained some subjects with a ventilatory defect but no sputum, or it contained some subjects who did not bring specimens of the sputum they were producing.

TABLE XI—RELATION BETWEEN WHEEZING AND PRESENCE OF SPIRALS IN SPUTUM
(Both winter specimens in males)

—		No spirals	Spirals	Total
Wheeze	Never ..	25	4	29
	Occasional ..	44	20	64
	Most days ..	29	7	36
	Total ..	98	31	129

$\chi^2=2{\cdot}21$. P=0·2 to 0·1.

The first explanation would be accounted for by the presence of a significant number of disabled men with "dry" bronchitis—i.e., a cough but no phlegm. There were 12 men in the whole group who admitted to cough but not to phlegm; of these only 5 produced empty containers (6 others produced sputum and 1 did not return the container) and these had an average M.B.C. above the mean for the asymptomatic group (Fletcher et al. 1959). Therefore, the discrepancy is not accounted for by the presence of "dry coughers".

TABLE XII—RELATION BETWEEN SICKNESS ABSENCE AND VOLUME OF SPUTUM SPECIMENS
(Both winter specimens in males)

—		Number of specimens		
		Volume nil	Volume less than 2·0 ml.	Volume over 2·0 ml.
Recorded respiratory illnesses	0	71	37	44
	1	21	8	13
	2 or more	6	4	19

$\chi^2=15{\cdot}4$. P=0·01 to 0·001.

On the other hand there were 7 men who admitted to sputum "all day" in winter who returned empty containers. Exclusion of these raises the mean M.B.C. of the "returned empty" group from 114 to 116. Exclusion of 2 additional men who had two or more chest illnesses in the past three years brings the mean M.B.C. up to 119. This is strong presumptive evidence that there were men in this study who were concealing both subjective and objective evidence of their respiratory disease.

Sickness Absence

The subjects were grouped into those who had had none, those who had had one, and those who had had two or more respiratory illnesses (excluding " influenza ") within the past three years. A highly significant relation between the volume of the sputum specimens and the frequency of sickness absence was found (table XII). The production of purulent sputum and sputum producing a heavy growth of *H. influenzæ* showed no correlation with the frequency of chest illnesses.

Discussion and Conclusions

Hitherto the prevalence of chronic non-specific pulmonary disease has been studied by death-rates, sickness-absence certification (Stuart-Harris 1954), and more recently by surveys of respiratory symptoms (Higgins 1957, Pemberton 1956). This study demonstrates that under favourable circumstances surveys of expectoration can also be made and may provide consistent evidence concerning the volume, macroscopic appearance, and bacteriology of the bronchial secretions of a large group of subjects. Our sputum findings correlated well with symptomatic investigations carried out on the same group of subjects and with the facts available about their respiratory disability and past sickness absence (Fletcher et al. 1959).

Of the investigations carried out on the sputum only the volume of sputum specimens is a significant index of the severity of respiratory disease as judged by objective tests or by answers to the questionnaire. The normal bronchial tree does not produce sufficient mucus for expectoration to occur; by this standard half of our men and a quarter of our women have abnormal bronchi. Although the bulk of the population and probably many doctors consider that a little mucoid sputum is the normal accompaniment of smoking, the production of purulent sputum is manifestly abnormal. Over the period of study a quarter of the men and an eighth of the women produced purulent sputum, indicating that they had persistent bronchial disease—probably chronic bronchitis.

Although there was a significant association between the presence of pathogenic organisms and the purulence of the sputum, neither was related significantly to the other indices of severity of the disease. This may indicate that bacterial invasion of the lower respiratory tract is a result and not the cause of the bronchitis, or that the presence of bacteria is important only during exacerbations. In larger populations bacteriological and microscopic investigations might yield more useful information.

The difference in the incidence between men and women, and the fact that the proportion of men affected rises with age may in part be due to differences in smoking habits (Fletcher et al. 1959). Further surveys of population-groups using symptoms, lung-function tests, and sputum examinations are needed to confirm our observations and to show the prognostic importance of expectoration.

Although the discovery of 1 case of sputum-positive pulmonary tuberculosis amongst 288 subjects may be a chance finding, it does call attention to feasible ways of finding pulmonary tuberculosis in the general populaton other than by repeated mass-miniature radiography.

Summary

The results of a study of the sputum specimens produced by two groups of the working population in London are reported.

The collection of specimens was part of a survey of respiratory symptoms, respiratory disability, and sickness absence-rates which is reported elsewhere. Carried out with the willing cooperation of the subjects, this collection revealed that about half the men and a quarter of the women were in the habit of expectorating. Those who produced specimens of more than 4 ml. in the first hour after waking had, on the average, a reduced indirect maximal breathing capacity, and a greater incidence of chest illnesses.

In the detection of chronic non-specific respiratory disease sputum collection is a useful and reliable adjunct to the method of survey by questionnaire. It might also be used in the detection of pulmonary tuberculosis.

The material used in the preparation of this paper was part of a study carried out with Dr. A. S. Fairbairn and Dr. C. H. Wood. The authors wish to thank the Post Office Authorities for allowing the investigation; the Union of Post Office Workers and the Civil Service Clerical Association for their help; and above all the subjects for their patient cooperation. They wish to thank also the staff of the bacteriology department of the Postgraduate Medical School for undertaking the sudden heavy load of investigation which was superimposed on their routine work.

REFERENCES

Capel, L. H., Smart, J. (1958) *Lancet*, ii, 771.
Elmes, P. C., Fletcher, C. M., Dutton, A. A. C. (1957) *Brit. med. J.* ii, 1272.
— Knox, K., Fletcher, C. M. (1953) *Lancet*, ii, 903.
Fairbairn, A. S., Wood, C. H. (1959) In the press.
Fletcher, C. M., Elmes, P. C., Fairbairn, A. S., Wood, C. H. (1959) In preparation.
Higgins, I. T. T. (1957) *Brit. med. J.* ii, 1198.
May, J. R. (1953) *Lancet*, ii, 899.
Pemberton, J. (1956) *A.M.A. Arch. ind. Hlth*, **13**, 529.
Stuart-Harris, C. H. (1954) *Brit. J. Tuberc.* **48**, 169.

Vaccination against Poliomyelitis

By the end of April over 1 in 4 in the 15–26 age-group in Great Britain had volunteered for vaccination against poliomyelitis, compared with only 1 in 12 two months earlier. The total had risen from 517,000 to 1,586,000. Of these, 600,000 had had two doses and a further 700,000 one dose. The acceptance-rate for children up to 15 years of age had risen to nearly 69%, compared with 63·5% at the end of February.

Infectious Diseases in England and Wales

Disease	Week ended May			
	9	16	23	30*
Diphtheria	3	3	2	3
Dysentery	1035	1067	718	943
Encephalitis:				
Infective	..	2	3	3
Post-infectious	4	7	4	3
Food-poisoning	285	244	208	280
Measles, excluding rubella	15,737	18,200	17,520	16,932
Meningococcal infection	19	24	18	24
Ophthalmia neonatorum	32	23	20	37
Paratyphoid fever	10	3	4	7
Pneumonia, primary or influenzal	303	336	279	232
Poliomyelitis:				
Paralytic	5	19	18	23
Non-paralytic	8	16	3	6
Puerperal pyrexia	197	223	158	208
Scarlet fever	1016	997	744	675
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	539	567	394	551
Meninges and C.N.S.	11	7	3	11
Other	66	64	67	61
Typhoid fever	7	4	..	..
Whooping-cough	649	611	465	627

* Not including late returns.

Special Articles

OUTPATIENT ELECTROPLEXY

Review of Work of a General Hospital Clinic

O. E. F. HODGSON
B.A., M.B. Cantab., D.P.M.
SENIOR PSYCHIATRIC REGISTRAR

M. SIM
M.D. Edin., D.P.M.
CONSULTANT PSYCHIATRIST

From the United Birmingham Hospitals

THOUGH the technique of electroplexy has not altered greatly since it was introduced some twenty years ago (Cerletti and Bini 1938), there have been some changes. Relaxants and anæsthetics are now used, nursing procedure and the number and spacing of the treatments have been modified, fewer physical contraindications are recognised, and psychiatric indications are more accurately defined. Its value in the treatment of depressive states is now almost universally recognised, though the adequacy of the original therapeutic trials has been questioned. Objections have been raised to its use on outpatients because of the possibility of too hasty assessment, less effective supervision, and physical hazard; yet more and more outpatients are receiving the treatment, modified with anæsthetic and relaxant, without mishap. It has been used at St. George's Hospital, London, since 1941 (Mallinson 1948) and more recently at mental hospitals and other clinics (Mezer and Solomon 1954, Craft 1958, Carse et al. 1958).

It is not surprising that general hospitals in populous areas with a tradition of outpatient care should have pioneered and developed this service. For ten years it has been provided by the Midland Nerve Hospital (a neuropsychiatric unit of the United Birmingham Hospitals), and we thought it opportune to review some of its clinical and social aspects.

The Birmingham Unit

Building and Staff

Our unit is in a converted old house near the city centre on a major bus-route. It has been used as an outpatient department, primarily for neurological patients, for about thirty years. The building and its environs are frankly unattractive: the interior has been improved as much as possible, but no major alterations have been made, because the building is due for demolition next year. The clinics are staffed by a consultant who selects and periodically assesses the patients and interviews the relatives weekly. A senior registrar carries out the actual treatment with the help of an anæsthetist for some selected cases. There are a sister, two State-registered nurses, a nurse in training, and a hospital porter. An untrained woman serves the patients with tea after their treatment and thus releases the nurses for more responsible duties. Clinics are held twice a week but supplementary treatment can be given at the inpatient department nearby. For all patients the treatment is modified with relaxant and anæsthetic.

Patients

During 1954–56, 364 patients were selected by one of us (M. S.) as suitable for outpatient electroplexy. Most were referred by their family doctors; some were seen at domiciliary consultations; and some were referred from a general hospital where they had been admitted for attempted suicide.

135 were women and 229 men. The 2 youngest patients were under twenty, the 6 eldest were between seventy and seventy-nine, and rather more than half were between thirty and fifty. 29 patients had already been in a mental hospital, 32 were considered to be serious suicidal risks, and a further 31 had attempted suicide. Of these 364 patients 79 did not complete the course of treatment.

Follow-up

All patients who completed the treatment were reviewed two months after their last treatment, and we tried to follow them up two years later, if possible by personal interview. If an interview could not be arranged we sent a questionnaire to the patient, and, if this was not returned, a letter to the general practitioner. Of those who completed the treatment we were able to trace over three-quarters. Bearing in mind the length of the follow-up (sometimes four years), and the large shift in the population of the area, this figure is about as high as can be expected.

Of the 285 patients who completed the course of treatment after two months, 204 were assessed as symptom-free, 82 had only minor symptoms, and 26 were not improved. After two years 68 of these patients could not be traced and 4 had died. Of the 213 we succeeded in tracing, 156 had remained well and 57 had relapsed. The table shows the number of treatments these patients received:

No. of treatments	Patients			Remained well for two years				Relapsed in two years			
	M	F	T	M	F	T	%	M	F	T	%
6	2	5	7	1	5	6	86	1	..	1	14
7	17	34	51	10	26	36	71	7	8	15	29
8	48	69	117	40	48	88	75	8	21	29	25
9	14	24	38	9	17	26	68	5	7	12	32

M = male. F = female. T = total.

Of the 35 patients who had had electroplexy in the two years before their course at our clinic, 14 (40%) relapsed, compared with a relapse-rate of 20% for the whole series.

Discussion

These findings show that many patients with major psychiatric illness can be successfully treated as outpatients, using electroplexy, modified with thiopentone anæsthesia, and a short-acting relaxant (' Scoline '). A disturbing feature of our series is the high attendance failure (nearly 22%). This is about double the figure given by Mezer and Solomon (1954), and on a visit to their unit in Boston one of us (M. S.) was impressed by the intensive social support available there. Perhaps our figure could be reduced if we made even fuller use of our psychiatric social workers. In our series the older patients and those in semiskilled jobs were less likely to finish the course of treatment. The distance a patient had to come to hospital made little or no difference.

A general-hospital unit which treats mental outpatients exposes itself to criticism, particularly from mental-hospital workers. Because it retains the voluntary hospital tradition of seeing patients from near and far, it may encroach on the catchment area of mental hospitals. Some critics further assert that many of its patients end in the mental hospital in any case, and would have been better off if they had been " properly " treated from the start. Our results refute this assertion. Of 215 patients followed up after two years only 18 had entered a mental hospital—a smaller number than the 29 who had been treated in mental hospitals before they came to us.

The number of treatments is still a matter for debate. In this series it varied from 6 to 18 (in one case). Kalinowsky and Hoch (1952) report that most depressives respond

to about 4 convulsions, but that it is usual to give a few more to stabilise the result "although the necessity for such additional treatment has not been proved". In one clinic Sargant and Slater (1954) reduced the average number of treatments per patient from 8 to under 4 "without any reduction of the recovery-rate on follow-up inquiry". Our table above shows a slightly higher recovery-rate in those who had 8 treatments compared with those who had 7 (75 : 71%) yet the patients who received 7 treatments had a better history, had responded more rapidly, and at the time of treatment were thought to have a more favourable prognosis. In a few response to treatment was slow. When no improvement was admitted by patient or relative after 6 or 7 treatments, we did not abandon the treatment but reassessed the patient's condition: if the general indication still held and there was no physical contraindication, the treatment was continued—with gratifying results. Our follow-up after two months showed that 92% of the patients had regained their previous level of activity, and that in carefully selected cases the immediate prognosis should be excellent.

Our patients were given electroplexy modified with thiopentone and scoline, and our results do not support the tentative hypothesis of Seager (1958) that patients respond less well to modified E.C.T. The relapses shown in our two-year follow-up are not unexpected, for some patients had illnesses, such as schizoaffective and paranoid states, which respond only temporarily to E.C.T. Though depressive states are the prime indication for E.C.T., a few run in cycles, and if the follow-up is long enough, recurrence will be recorded as relapse. Our figures confirm to some extent the findings of Gold and Chiarello (1944) and Schiele and Schneider (1949) that patients who already had had breakdowns, and therefore had a less satisfactory pre-morbid personality, fared worse than those who had not been treated before.

In all, during the period of study, 2600 treatments were given; and, apart from one unusual case of hæmorrhage from the ear, alleged to be due to tearing of the tensor tympani, there were no ill effects directly attributable to the treatment. Of our patients 17% were suicidal (either attempted or a serious risk). There was no record of suicide during treatment or after it in any patient who completed the prescribed course, but 1 patient who interrupted her treatment did attempt suicide three years later. A severe depressive illness, therefore, is in itself no bar to outpatient electroplexy.

REFERENCES

Carse, J., Panton, N., Watt, A. (1958) *Lancet*, i, 39.
Cerletti, V., Bini, L. (1938) *Arch. gen. Neurol. Psichiat.* **91**, 266.
Craft, M. (1958) *Lancet*, ii, 149.
Gold, L., Chiarello, C. J. (1944) *J. nerv. ment. Dis.* **100**, 577.
Kalinowsky, L., Hoch, P. (1952) Shock Treatment, Psychosurgery, and Other Somatic Treatment in Psychiatry. New York.
Mallinson, W. P. (1948) *Brit. med. J.* ii, 641.
Mezer, R., Solomon, H. (1954) *New Engl. J. Med.* **250**, 721.
Sargant, W., Slater, E. (1954) Introduction to Physical Methods of Treatment in Psychiatry. Edinburgh.
Schiele, B., Schneider, R. (1949) *Dis. nerv. Syst.* **10**, 291.
Seager, C. (1958) *J. ment. Sci.* **104**, 206.

Occasional Book

INDEPENDENCE AND AUTHORITY

IT is impossible to picture organised society without an "establishment"—indeed, without a system of political, religious, literary, medical, and other establishments—and it is difficult to think of an age when such establishments have not been the targets of bombs, wit, venom, or ridicule. Looking around us—as well as looking back—it is easy to see why. Though characteristically disinclined to selfcriticism and incapable of admitting their limitations, members of establishments tend to be pompous; they are often petty; sometimes they are dim; and they have been known to be vicious. Their critics, on the other hand, though generally bright and passionately addicted to castigating themselves, also have their blind spot: they rarely perceive behind the impersonal facade which they attack, the repository of past generations' intensely personal endeavours, experiences, and suffering. It is unfortunate for both sides that, whereas debunking has always attracted the young and articulate, spokesmen of the debunked rarely venture beyond the platitudinous. To the uncommitted (if such exist) this makes for dull combat; and it may be a reason why history often appears as a succession of disasters—whether disguised as victory or as defeat—rather than as a conflict of balanced forces. Observers of the contemporary medical scene, however, have no cause to grumble: they can listen to at least one champion of established values who has always dared to say what he thought and who always knew how to say it superbly well. In his latest volume of collected essays Sir Heneage Ogilvie [1] again proves himself master undebunker of his generation.

"To preach idleness to the medical student would be like taking coal to Cardiff or penicillin to St. Mary's. The medical student is, in this respect, a far wiser being than I am. He has studied the ætiology of stress diseases and has decided that they are not for him. He has developed a defence mechanism against overwork that is proof against the attacks of parents, or deans, or the more insidious infiltrations of conscience. To the medical student, therefore, I must preach the gospel of work."

And wonderful preaching it is too. He castigates the "society" psychiatrist, those "hyenas of Harley Street, the confidence men of medicine, who trade the goodwill and trust established by generations of honest men, who gamble on the magic of an address as able to suggest long training and established position". And in his contempt of what he regards as a symptom of the modern apotheosis of the Common Man he is prepared to go further.

"Even making every allowance for those who have prostituted their teachings, is the world a better place because Freud and Adler inhabited it? Is it the cleaner and the nobler for the ministrations of their more fanatical disciples? Is justice better served because they flock to the Law Courts to explain why every thug in the dock is more sinned against than sinning? I am not sure. The sinner who formerly turned to the Rock of Ages saying 'Cleanse from guilt and make me pure', now turns to psychiatry pleading 'Explain away my guilt by attributing it to some complex for which I am not responsible, and allow me to go on being impure without any longer being ashamed of it."

It is, of course, idle and irrelevant to speculate whether the world is a better or a worse place for having been inhabited by Freud. Nor need one take too seriously Sir Heneage's pronouncements on such far-flung topics as G. B. Shaw, modern sculpture, or the Labour Party: his little hates are not without a certain period charm which would have delighted most of his targets. But the tradition to which random quotations can do no justice, but which the best of these essays faithfully reflect, remains both fascinating and relevant. At the professional level it has animated for a hundred years or more the labours of many of the greatest figures in British medicine; and it animates many still. It is in this tradition that Sir Heneage himself—probably not the last and certainly not

1. No Miracles among Friends. By Sir HENEAGE OGILVIE. London: Max Parrish. 1959. Pp. 176. 18s.

the least in the line—has turned his mind to some of the most baffling surgical problems of his age; and time and again he has crystallised in a phrase the shapeless nebulæ which often pass as " the surgical thought " of the day. Much of what he has taught—ranging from shock and cancer to hernia and hæmorrhoids—was bold and original when first propounded; and it is a measure of his powers of intellectual penetration that most of it has become part of orthodox surgical teaching—indeed (Freud or no Freud) part of the surgical subconscious. Apart from his incisive mind and unique command of English, the quality which has, above all, enabled him to do this is complete fearlessness; and, whatever may be the limitations of the surgical tradition which he represents, his aristocratic indifference to the clamour of the profane is surely something which we should try to preserve.

It is impossible, however, to separate the surgical from the human elements of this tradition; and it is the undebunking of human values which rouses Sir Heneage to the heights of eloquence. These values are " Victorian " only because they were greatly admired by a comparatively narrow but influential section of late-Victorian society and bitingly ridiculed by succeeding generations. In essence they are the virtues of republican Rome—not, perhaps, of the State as it actually existed but as it has been portrayed by historians, politicians, and public-school headmasters from Tacitus to the present-day disciples of Dr. Arnold. The Greeks, Sir Heneage admits, gave the world imperishable marvels of art, literature, and science, all within the space of fifty years (whereas one is hard put to find any trace of such a legacy after five hundred years of republican Rome); but the Greeks " were unable to sink their independence as individuals to combine against the common enemy, and their history is one of subservience to less gifted but better disciplined races ". In the eyes of " Romans " of all ages, races, and professions Plato, Hippocrates, and the glades of Olympia cannot atone for this inability to " combine independence with authority "—a failing made all the more grievous by the happy insouciance of the subjugated.

This conflict of aspirations is highly topical. In medicine we are witnesses today of the Cult of the Original. What began as a modest attempt to secure a place in a backward-looking profession for a handful of incorrigibly original minds has grown into an all-pervading obsession. It now compels young doctors who aspire to the modest independence of consultant status to fritter away years of their training in applying safe, sound (sometimes brilliant), but blessedly unoriginal minds to the pursuit of original research. Originality is irrepressible: it can neither be encouraged nor discouraged; it cannot be switched on and off for the purposes of higher degrees; and, fortunately, it is exceedingly rare. " Politics, industry, science . . . and, above all, medical research . . . all need ' yes-men ' in the proprotion of perhaps fifty to one leader ", Sir Heneage believes; and in an age when yes-men are becoming as scarce as geniuses used to be, many will echo his sentiments. But in warning and guarding against one extreme we must never lose sight of the other. If the worship of mock originality is as crazy and, one hopes, as ephemeral as most extremes of fashion, the pressure to real conformity is a perennial and terrible danger: in medicine, as in other pursuits of life, we walk in the shadow of the *Führerprinzip*. At this point, however, the word should pass back from the Establishment to the Rebels.

MAGOG

In England Now

A Running Commentary by Peripatetic Correspondents

I AM no morbid anatomist, but I have always been deeply impressed by tales which reach my ears, mostly in reverent whispers, about medicolegal pathologists—about their speed, their technical virtuosity, their capacity for minute observation, their almost unbelievable powers of deduction which hold judges spellbound, give pause to the boldest of Q.C.s, and even command the grudging respect of coroners, and about the fabulous incomes they are reputed to earn. At last the day came when one of the supermen was expected at the hospital to do a P.M. on a case which even the neurosurgeons—those other supermen—had failed to save. At last I should see for myself. But it was not to be. " No, there isn't enough room in the P.M. room " they said firmly, " You just look after the shop while we're away. Come on boys, we mustn't be late." Silence fell on the department. But not for long. Soon a breathless assistant came rushing back. " Quick, he wants an adjustable spanner. No, not that, a small one, smallest you've got." " What on earth . . .", but the messenger was gone like a flash. When the department reassembled for tea, wonder at what they had witnessed filled their eyes and held them speechless. I just couldn't bring myself to break the spell. So I am still wondering. The only explanation I can think of is that, fashions changing as they do, the neurosurgeons have abandoned stitches and taken to nuts and bolts.

* * *

When practising in a new country one can expect difficulties with language, even when the new country happens to be English-speaking. Here in Newfoundland the West of England origin of many people is apparent in their speech as well as in their names, but, although I am familiar with the West Country, I had much to learn when I came out here.

" My man has got the kitches, doctor ": this describes the pain of pleurisy that " kitches " you when you breathe. Usually to be taken seriously, as the word is used with some discrimination, and is not applied to any old pain in the chest, but only to this particular pleural pain. Urticaria " rises out all over " and is then described as " the hives ", whereas " the bunches " are small skin tumours or swellings. " Covered all over in bunches " would, of course, make one think of von Recklinghausen's disease. After three months I felt that I was getting the hang of things, but last week I was caught again. I do not know why, but I have always felt mildly irritated by the patient who walks into the surgery and says " Doctor, I've got a slipped disc ". Here the patient presents with similar symptoms but says instead " Doctor, it's the purity stitches ". Now that I recognise the term I like it well; and one cannot help but feel properly sympathetic towards an unfortunate whose troubles have such an obviously worthy ætiology.

* * *

If I wanted the job, I knew that I should have to plan in advance. By careful questioning I learned that my prospective employers preferred candidates with qualifications a little out of the ordinary. I borrowed a bassoon from a friend and bought a book called *Bassoon Playing Made Easy*. It didn't make it very easy, but after much effort I mastered the first steps on the unwieldy instrument, and felt that I was prepared for the interview.

It didn't go too well at first. They seemed bored and uninterested. At last the chairman wearily tossed across the usual question: " And have you any particular interests, Doctor? " " I'm learning to play the bassoon," I answered quietly.

" Why on earth the bassoon? " someone said, sitting up. " I've always wanted to play it," I replied, and a discussion began on the merits of wind instruments in general, and the bassoon in particular. I sat back and let them get on with it, throwing in a remark from time to time so as to hint at the vast musical potential that lay hidden in me. At the end of

the interview I felt at least that they would remember me, and was well satisfied.

I got the job. I think, on the whole, I deserved it. My only problem now is that no-one believes me when I say modestly that I haven't got very far with the bassoon. All my colleagues are awaiting complimentary tickets for my Wigmore Hall début.

* * *

A middle-aged farmer who had developed a lymphangitis on a Sunday came to see me while I was busy in the garden. The local doctors, he told me, were not at home, so would I see his arm? I explained to him why, as a school medical officer, I should not treat him and advised him to motor into the neighbouring town to consult the doctor there. He was back within the hour, saying that the other doctor was not on duty. So I looked at his arm, dressed the festering finger, and gave him penicillin (which I just happened to have in my bag). He called again on Monday. He was delighted with his quick recovery and wanted to know how much he owed me for my services. I explained again that I could not accept any payment because as a local-authority employee it would be improper for me to take payment for services I had no right to give. When he insisted, I had to be firm in my refusal. At last a light passed across his face and he left saying "I'll fix you!". We finish work at 5 P.M. and by 5.30 I was getting into my garden, when I noticed my farmer friend waving to me as he drove up in his tractor. In next to no time he and his workman had dumped a large load of manure over my garden wall. As he drove away he shouted to me. "That jolly well fixes you, doesn't it?"

* * *

I should feel happier about the outcome if I really knew what is wrong with the chap.

I am not a mean man, but I confess that I was delighted when an ex-patient, a factory-trained mechanic starting his own back-street garage, offered to overhaul and recondition my elderly, but not decrepit, Bentley. I expected slow progress, but after some weeks thoughts of the eviscerated, dismantled engine began to intrude at unsuitable moments during teaching rounds, outpatients, or conferences. So, back from a few days' visit to another centre, I went round to the garage to assess progress. The dismembered car was still there, but not my patient. "He's back in hospital in your ward; didn't you know?" said his son.

I rushed back to hospital with the anxious haste of a man expecting bereavement and my fears were justified. He lay in bed, rather disgruntled, exhibiting a bizarre assembly of symptoms and signs which have baffled me and have even fooled my registrar, who knows a lot about queer syndromes. Today he said that he would like to try a trip to Lourdes. My intellectual resources are exhausted and his proposition appealed. I wonder whether I could ask him to intercede on behalf of the Bentley?

* * *

ATOMIC COMIC

Monsters bearing mutant genes,
Chimæras wearing borrowed spleens—
My horror comic often features
Such bizarre atomic creatures.

Funny beasts are rather nice
If they're guineapigs or mice.
But isn't it grim to think of persons
In weird variety of versions?

When you reflect on these diseases,
Blood runs cold and marrow freezes.

Scientists, please, you shouldn't smile!
That stuff you're handling is fissile.
Criticality tricks and capers
Get your names into the papers.

Freezing marrow did I mention?
Yes indeed—that's the intention.
If safety margins get too narrow
You'll be *needing* frozen marrow!

Letters to the Editor

ROUTINE MEDICAL EXAMINATION OF EXECUTIVE STAFF

SIR,—The value both to the firm, who pays for it, and to the individual employee, of the so-called "top executive medical examination" is at present being discussed in medical and industrial circles.

In America it is a procedure widely adopted by firms and individuals. Here, although it has been condemned as useless by many senior members of the profession, routine medical supervision is, in fact, being instituted by an increasing number of organisations for their staff.

It is thus of the utmost importance, to guide both medical and industrial thinking, that an attempt should be made to assess, as objectively as possible, the value of these examinations. In such an assessment, the difficulty is always to find a suitably simple yardstick, applicable over a wide range of both patients and procedures.

We are proposing an investigation in which any doctor, working either individually or as a member of a clinical or industrial team, can participate. A record card has been designed to be filled in "post hoc" on any patient examined. Apart from some basic data on the patient, and the scope of examination and investigations (this can, in fact, be filled in by a secretary) the card seeks to record the new significant diagnoses thrown up by this particular examination.

In terms of preventative medicine, the procedure can only be recommended to a firm or to a patient if, by early diagnosis, prognosis is improved. This is the yardstick we are proposing, to measure the usefulness of this type of examination.

Additionally, it is of interest and value to know how the diagnosis was reached—i.e., the contribution made to it by each procedure such as chest X-ray, E.C.G., &c. An attempt to assess this is also being made.

Although it will involve participants in additional work, this work can be done after dealing with the patient, and we think that the investigation will be both interesting and valuable.

Any number of doctors doing a large or a small number of examinations annually can join the scheme, which, by pooling the experience over a wide range of patients and procedures, should give us a valid and objective assessment of the value of the examinations.

Details will gladly be sent to any interested potential participant who writes to the Medical Research Unit of the Institute of Directors.

Medical Research Unit,
Institute of Directors,
10, Belgrave Square,
London, S.W.1. H. BERIC WRIGHT.

Medical Consultant,
Rolls Royce & British
Commonwealth Shipping Co. ARTHUR LEVIN.

DRIED SKIM-MILK DISTRIBUTION IN UGANDA

SIR,—Your columns have lately contained two references [1 2] to the use of protein supplements in underdeveloped countries. In his article on Uganda [2] Dr. McFie mentioned that I had begun to use skim-milk powder in a child-welfare clinic; I should like to give the results of the first six months' experience.

At the end of May, 1958, a consignment of dried skim-milk powder was received from Church World Service in America for distribution in child-welfare clinics in Mengo District, Uganda. Some was distributed by the missions and the Government, and some by the Child Welfare Unit (Uganda Medical Department). The aims were to give a practical basis for nutrition teaching in child-welfare clinics, to observe its effects on the growth and health of children aged between six

1. Williams, C. J. *Lancet*, 1958, i, 863, 919.
2. McFie, J. *ibid.* 1959, i, 91.

months and six years, and to stimulate a market for locally produced dried skim-milk powder.

Milk powder was distributed at nine centres in the Kampala area; in some centres distribution was monthly and at others fortnightly or weekly. All children aged between six months and six years (2057 children) were given an allowance of 2 lb. monthly (8 oz. weekly). Children treated for malnutrition (45 children) were allowed 4 lb. monthly (1 lb. weekly). Most children started to receive dried milk during their sixth month, but a very few (11) were given skim-milk powder to use with porridge, mashed banana, &c. before they were five months old if the mother's breast milk seemed insufficient.

Skim-milk powder was never used for artificial feeding. When artificial feeding was necessary the parents were advised to obtain fresh milk. It was necessary to emphasise that the skim-milk was not suitable for very young babies, and constant vigilance was needed to make sure that milk issued to older children was not mixed with tea and put in a bottle for feeding the baby. Parents were never advised to try to reconstitute the milk powder with water but rather to mix it up with porridge, mashed banana, fruit purée, sweet potatoes, matoke (plantain), or any other suitable food.

The most immediate result of the milk distribution was that attendance at child-welfare clinics doubled.

The average number of attendances monthly before starting dried skim-milk distribution was 1000, and after starting milk distribution the number increased to about 2000. This was largely due to increased regularity of attendance, although there was also an increase in the number of first attendances. There was also a change in the spirit of the clinics: nutrition teaching became a practical matter and parents became enthusiastic and appreciative.

Another result of the free skim-milk distribution was that it became possible to treat children with kwashiorkor without referring them to hospital unless they were severely ill.

Between June and December, 1958, a total of 20 children were seen with kwashkiorkor who were considered suitable for outpatient treatment. Of these, 15 attended more or less regularly for from three to six months and all made excellent progress.

As might be expected, the results were not so good in underfed children, such as babies suffering from the effects of breast-milk insufficiency from the first few weeks of life. Such children were often seen for the first time at the age of nine months to a year, when they usually weighed about half the expected weight for their age, and abdominal distension was severe. At the child-welfare clinic treatment was first directed against any infections or ascariasis, prophylactic chloroquine was given weekly or fortnightly, and an allowance of 1 lb. weekly of skim-milk powder was given. The parents were advised to give the child at least three meals daily consisting of skim-milk powder mixed with maize porridge, mashed banana, or soup. 25 children were treated in this way, but in spite of treatment 10 (including 3 pairs of twins) failed to thrive and had to be referred to hospital.

The effect of routine milk supplementation was encouraging. All the mothers whose children were receiving milk regularly were unanimous in their appreciation. Although both they and the clinic staff thought they could see a difference in the children's condition, the effect was difficult to assess objectively. Since it was not possible to have a control group of any kind the only basis we could use for comparison was the progress of the same children during the preceding six months.

Unfortunately there was a shortage of staff at the clinics, particularly during the middle of the year, and for this reason the only measurements or observations available for comparison were the weight increments of the children before and during dried-milk distribution: from December to June (no milk) and from June to December (milk). For this comparison records were used of children who had received over 7 lb. skim-milk powder and who were aged from two to six years. Records of children whose weights were affected by severe infections or malnutrition were not used. The differences in weight increment before and during skim-milk supplementation in 163 children were as follows:

Average weight increment from December to June before milk distribution	1·61 lb.
Average weight increment from June to December during milk distribution	2·47 lb.
Average difference between first and second weight increments	0·85 lb.

Although in general the results of dried skim-milk distribution were extremely satisfactory, it was also true that a great deal of milk powder was apparently wasted. The numbers of children and the quantities of milk which they received were as follows:

Children who received 1 lb. or less milk powder	547
" " " 1–5 lb. " "	482
" " " 5–10 lb. " "	490
" " " 10–12 lb. " "	228

Thus just over a quarter of the children received 1 lb. or less of milk powder, a quantity which could not be expected to have any effect on the child's health, and only just under half of the children received a really useful quantity (over 5 lb.). Nevertheless one of the aims of the distribution was to stimulate a demand for locally produced skim-milk powder, and no doubt the distribution of free samples was one way of doing this. The next step will be to encourage improvements in the marketing and advertising of the local product.

Child Welfare Unit,
Kampala, Uganda. H. F. WELBOURN.

OCCUPATIONAL THERAPY IN MENTAL HOSPITALS

SIR,—In view of the syllabus for mental nursing and the appreciation of the General Nursing Council of the part occupational therapy has to play in the rehabilitation of the mentally ill, it seems that a new approach to the problem of providing occupational therapy has become necessary.

In my experience most medical superintendents want to see work done on the wards, so much so that if therapists cannot provide it, they want the nurses to do so. With the cooperation of the medical profession, the G.N.C., and the Association of Occupational Therapists, I suggest that in a suitable hospital a ward of long-term patients be put entirely under the control of occupational therapists, working under the direction of the medical staff.

The occupational team should have the same number as nurses normally required to run the ward. It should be chosen from occupational therapists who are already trained nurses, or, if such therapists are not available, nurses who have shown themselves interested and capable in handicrafts. College-trained therapists should also be part of the team.

The team would be responsible for all duties associated with daily living, and also occupational therapy, including social and recreational activities, it being understood that only mentally ill patients are to be dealt with.

If, as I believe it would, this approach to keeping patients actively engaged and working towards their own cure or improvement met with greater success than present methods, then I suggest that the bodies concerned should cooperate to produce a syllabus of training that would staff our mental hospitals on many wards with "occupational nurses", or therapists capable of nursing duties.

This does not mean that the nurse, as such, has no place. She would be required for the sick wards and treatment wards, but the "occupational nurse" would be trained to recognise whether the patient had some physical complaint.

A syllabus of training for the occupational nurse would comprise craftwork training as already given to student therapists, anatomy, physiology, first-aid, medicine, psychology, and

psychiatry, and in addition practical training in the nursing duties of daily living and experience on the ward.

After two or three years' practice as assistant, the occupational nurse should be capable of holding senior positions, and running an occupational therapy department distinct from the ward.

Those who received this training would have to be prepared for shift work, thus seeing the patients at all times, and also be prepared for some of the less pleasant tasks which have always been a part of nursing.

My suggestions do not of course apply to general or orthopædic hospitals, where it seems to me the present arrangements are quite satisfactory.

I think the approach I have outlined would give a much better service to the patients, and would remove the discord which can creep in when two professions overlap.

Prestwich Hospital,
Manchester. HAROLD KELLAND.

HEADACHE OF MUSCULAR ORIGIN

SIR,—We agree with Madame Rudé (March 28) that headache of muscular origin is one of the commonest seen by the general practitioner as well as by the general physician and neurologist.

The use of massage is often unquestionably of the greatest importance in relieving such patients but, as emphasised by Madame Rudé, this form of treatment is only symptomatic. We should like to report another approach directed more towards ætiology which is applicable in an astonishing large number of chronic headaches.

In 1956 we reported the results of treatment [1] in cases of longstanding headache with clinical signs of dysfunction of the temporomandibular joints. Our favourable results were due to the restoration of more physiological conditions in the masticatory muscles. During the past few years we have extended our study to cases with chronic headache where it is possible to find out that the patient is an " addict " to habitual teeth-grinding or teeth-clenching (bruxism). This is a common condition among most nervous hyperirritable persons, especially during sleep, but also during periods of increased tension or stress situation in general. Usually, the patient is quite unaware of his habit and at first the doctor's suggestion is often denied as ridiculous. Very soon, however, the patient, after consulting husband or wife, is able to report that the suggestion was correct.

Bruxism can be diurnal in patients engaged in meticulous and precise work or while concentrating on important activities. More often it is nocturnal and the patient wakes with frontal headache which may also be in the temples and sometimes also along the origin of the masseter muscles. Clinical signs confirming bruxism are grinding facets on the biting surfaces of the incisors, hypertrophy and tenderness of the masseter and temporal muscles, and, more rarely, impressions on the front parts of the tongue as a consequence of pressing of the tongue against the teeth.

In an attempt to break this vicious circle we have used a special relaxation splint.[2] This plastic splint is essentially a modified Hawley splint which increases the distance between the jaws anteriorly. Thus the mandible is kept in the rest position and the patient finds it impossible to clench his teeth with full strength. Consequently the masticatory muscles relax, and, after some days or weeks, the headache gradually disappears. The splint is worn at night if bruxism is most pronounced then; otherwise it is worn also in special stress situations during the day. A few months after the headache has subsided the splint may be permanently removed, to be used afterwards only if headache recurs.

Since 1956 we have treated 55 patients with this syndrome and have obtained complete relief in 65%; 13 patients (24%) were considerably improved, complaining of occasional slight headache only, and 6 patients (11%) were uninfluenced by the treatment.

Central County Hospital,
Falköping, Sweden. RAGNAR BERLIN
LEOPOLD DESSNER.

1. Berlin, R., Dessner, L., Åberg, S. *Acta med. scand.* 1956, **50**, 129.
2. Dessner, L. *Svensk tandläk. Tidskr.* 1959 (in the press).

TRIFLUOPERAZINE AND IMIPRAMINE

SIR,—I should like to inquire whether any psychiatrist can tell me where to find a report on an adequate statistically controlled trial of trifluoperazine (' Stelazine ') and imipramine (' Tofranil ') which over the past few months have received a tremendous amount of publicity.

As far as I know, there has not been a single controlled trial reported in the literature concerning tofranil, and the only one I can find in regard to trifluoperazine is an inadequately reported trial by Rudy et al. in the 219-page book on the drug published by Lea and Febiger.

Whether these drugs will have any ultimate place in psychiatry no-one can say, but I feel I must enter a protest about the way in which such powerful drugs have been issued without their first being subject to adequately controlled trials.

Powick Hospital,
near Worcester. A. M. SPENCER.

TRAUMA AND SQUAMOUS SKIN CANCER

SIR,—It seems a pity to belittle the fortitude of Dr. Bray's old gardener (April 25, p. 888) in excising his own carcinoma, but it seems possible that this, and the other cases described by Dr. Ward Gardner (April 11, p. 760) were not carcinomas but rather mollusca sebacea (kerato-acanthoma).

As Dr. Lonkar (May 30, p. 1152) observes, molluscum sebaceum is easily mistaken, both clinically and histologically, for skin carcinoma.[1] The history is much shorter, for a molluscum sebaceum grows to the size of 1–2 cm. diameter in 4–8 weeks, while a carcinoma takes many months to attain this size. It occurs most commonly on the face, ears, and neck, less commonly on the arms and hands, and occasionally on trunk and legs, and the principal age of incidence is 40–70 years. Whittle and Lyell [2] have stated that " the histological features invariably suggest to the pathologist—unless he has been forewarned—the diagnosis of well differentiated keratinising squamous carcinoma ". The lesion is cup or flask shaped, filled with keratin, and lined by acanthotic epidermis with characteristic large prickle cells with pale washy cytoplasm. A typical feature in the cross-section is the finger-like appearance of the lip of this cup where normal epidermis covering the outer aspect is sharply reflected to become the acanthotic lining of the keratin-filled cavity. A dense mixed inflammatory infiltrate disrupts the lower epidermis and destroys separate clumps of squamous cells invading the dermis, while the prickle cells in the more superficial layers are orderly and mature. As the lesion heals the " cup " opens out and the keratin plug or horn falls off. It is this process that was probably hastened by the old gardener's penknife! The lesions in Dr. Ward Gardner's cases had the short history and occupied sites common for molluscum sebaceum. Their association with trauma has led me to review the incidence of trauma in the history of molluscum sebaceum.

Although Rook and Whimster [3] mentioned that all 29 of their cases had a history of trauma a few days before the lesion was first noticed, the possibility of preceding trauma is seldom discussed in the papers on molluscum sebaceum. One of Whittle and Lyell's [2] two cases followed injury; Calnan and Haber [4] mention preceding mild trauma in 3 out of their 105 cases; Grinspan and Abulafia [5] noted previous trauma in 11 out of 20 cases; and in 12 cases whose lesions have been sent

1. *Lancet*, 1958, i, 1212.
2. Whittle, C. H., Lyell, A. *Brit. J. Derm.* 1952, **64**, 424.
3. Rook, A., Whimster, I. *Arch. belg. Derm. Syph.* 1956, **6**, 137 (cited by J. M. Purdy. *N.Z. med. J.* 1953, **52**, 191).
4. Calnan, C. D., Haber, H. *J. Path. Bact.* 1955, **69**, 61.
5. Grinspan, D., Abulafia, J. *Cancer*, 1955, **8**, 1047.

to me for histological examination, preceding injury at the site of the lesion has been recorded in 3 (knocked hand, cat scratch on wrist, irritation behind ear by wire spectacle hook).

It is clear that in considering the incidence of trauma preceding squamous skin carcinoma, care must be taken to exclude all possible mollusca sebacea.

Ancoats Hospital, Manchester. ROGER GILLETT.

AMPHENONE AND RENAL FUNCTION IN HYPERTENSIVES

SIR,—The acute lowering of the blood-pressure by ganglion-blocking agents has been noted to result in a retention of sodium and water which is not obviously explained by alterations in renal hæmodynamics.[1–4] Previous work from this institution has supported this observation, and the possibility that this might be due to an increased activity of the adrenal cortex as part of a response to stress was suggested.[1]

The possibility of an adrenal response to the acute lowering of the blood-pressure as an explanation for the retention of sodium and decreased urine volume is being further investigated here. We considered that amphenone might be useful to test this hypothesis, because it suppresses adrenocortical steroid synthesis.[5] It has been suggested that in subjects with relatively normal adrenal cortices a compensatory increase in the production of endogenous adrenocorticotrophic hormone may prevent the drug from causing a decrease in the output of 17-ketosteroids and 17-hydroxycorticoids.[6] Aldosterone production is reported to be less affected by pituitary influence, and the effect of amphenone in decreasing the aldosterone levels does not appear to be overcome by increased pituitary activity.[7] Adrenal cortex action causing sodium and water retention might be overcome by the use of amphenone to block the production of aldosterone. Studies are under way on hypertensive patients in whom the sudden lowering of the blood-pressure is obtained by intravenous hexamethonium chloride. Amphenone is then given to decrease the activity of the adrenal cortex. In view of the potency and toxicity of amphenone the number of patients who can be investigated is limited. The present brief report concerns two hypertensive patients who have been investigated by acute lowering of the blood-pressure with hexamethonium chloride before and after the administration of amphenone.

—	Case 1				Case 2			
	Day 1 (control)		Day 2 (amphenone 10 g.)		Day 1 (control)		Day 2 (amphenone 5 g.)	
	A	B	A	B	A	B	A	B
$Na_{G.F.}$ (%)*	2·5	0·1	3·1	0·2	2·2	0·2	2·2	0·1
Serum-Na (mEq./l.)	143	143	140	139	141	140	142	142
Serum-Cl (mEq./l.)	104·4	..	104·7	107·3	106·2	107·1	104·3	105·9

A = before lowering the blood-pressure.
B = after lowering the blood-pressure.

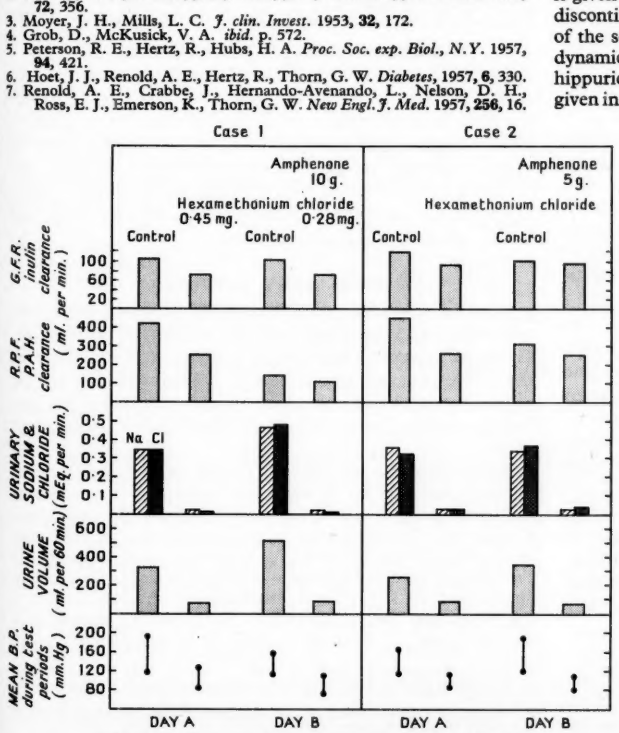
* $Na_{G.F.} = \frac{U_{Na}V}{P_{NaCl_N}} \times 100$

Methods

Patients are selected, after suitable investigation, who are considered to have essential hypertension. They are placed on a known dietary intake of sodium, and are studied on two experimental days with one week's rest between. On each of the two days renal-function studies are carried out during three consecutive twenty-minute periods before and after the lowering of the blood-pressure by intravenous hexamethonium chloride. The dose of hexamethonium given is estimated from the response of the blood-pressure, and is designed to lower the blood-pressure to normotensive levels within one hour or less. Procedures are identical on the two experimental days except that for twenty-four hours before the second day amphenone is given orally in amounts of 5·0–10·0 g. in divided doses, and is discontinued immediately after the procedures on the morning of the second experimental day are completed. Renal hæmodynamics are determined by measuring the inulin and *p*-aminohippuric acid (P.A.H.) clearances. The inulin and P.A.H. are given in suitable priming doses, and then in a sustaining infusion at a known rate by means of a constant infusion pump. After the priming doses of inulin and P.A.H. have been given and the sustaining infusion begun, an equilibration period of one hour is allowed. Three consecutive twenty-minute urine samples are then obtained through an indwelling catheter, and the bladder is washed out with distilled water after each sample is taken. These three twenty-minute collection periods serve as a control on each experimental day, and then three further twenty-minute periods are obtained after the blood-pressure has been lowered. Venous blood is withdrawn from the antecubital vein at the midpoint of each twenty-minute period. Inulin and P.A.H. clearances, serum and urinary sodium, potassium, and chloride levels, and urine volumes are then determined for each of the six twenty-minute periods. The values for each of the two groups of three periods are then averaged. Unfortunately, accurate urinary potassium values could not be obtained in these two cases owing to microscopic hæmaturia occasioned by catheterisation. Serial blood-pressures are obtained during the procedure by means of a sphygmomanometer, and the results are averaged for each period.

Results

The results are summarised in the accompanying figure and table. After the blood-pressure has been lowered there is a distinct decrease in the urine sodium and chloride, and in the urine volume, accompanying a less marked decrease in the



Urinary findings and blood-pressure in cases 1 and 2.

1. Lewis, J. A., Ramsay, A. G., Stevenson, J. A. F., Derrick, J. B. *Canad. med. Ass. J.* 1956, **75**, 184.
2. Ramsay, A. G., Derrick, J. B., Lewis, J. A., Stevenson, J. A. F. *ibid.* 1955, **72**, 356.
3. Moyer, J. H., Mills, L. C. *J. clin. Invest.* 1953, **32**, 172.
4. Grob, D., McKusick, V. A. *ibid.* p. 572.
5. Peterson, R. E., Hertz, R., Hubs, H. A. *Proc. Soc. exp. Biol., N.Y.* 1957, **94**, 421.
6. Hoet, J. J., Renold, A. E., Hertz, R., Thorn, G. W. *Diabetes*, 1957, **6**, 330.
7. Renold, A. E., Crabbe, J., Hernando-Avenando, L., Nelson, D. H., Ross, E. J., Emerson, K., Thorn, G. W. *New Engl. J. Med.* 1957, **256**, 16.

glomerular filtration rate (G.F.R.) and renal plasma flow (R.P.F.). If the sodium excretion fraction ($Na_{E.F.}$) is considered, it would seem evident that the decrease in the urine volume and urinary electrolytes cannot be accounted for completely by the decrease in filtration after lowering the blood-pressure. These decreases are apparent both on the control day and after the administration of amphenone. We have not yet measured aldosterone levels to assess the effect of amphenone. However, a comparison of the urinary sodium excretion and the urine volumes in case 1 shows a well-defined increase in those values after amphenone administration. This suggests a response similar to that noted by others after the administration of amphenone in effective doses,[7] and is considered to be due to a decrease in aldosterone levels. The response of the urine electrolytes to lowering of the blood-pressure was similar before and after amphenone administration. This indicates that an adrenocortical response is not a primary factor in causing the changes observed after lowering the blood-pressure. More intensive study is proposed to investigate further this observation.

P.A.H. is considered to have a diuretic effect and to increase the excretion of sodium.[3 8] In the present cases the direction of the changes was opposite to that expected from the P.A.H. effect; moreover, the plasma levels of P.A.H. were not high as is the case when the maximal rate of tubular excretion ($Tm_{P.A.H.}$) is being considered. Comparing the P.A.H. clearances during the control periods on the two experimental days, it appears that there is a decrease in the clearance of P.A.H. when amphenone is given. Possibly this may represent an effect by amphenone on the renal tubules which inhibits the excretion of P.A.H., and may result in erroneous values for the R.P.F.

Amphenone is a potent and highly toxic drug. No serious side-effects were noted in the two present cases, which were closely observed for any untoward reaction.[9] The 1st patient, who had the 10 g. dose of amphenone, showed some decrease in the basal blood-pressure during the twenty-four hours of amphenone administration before the second experimental day. It was further noted that the amount of hexamethonium required to cause the desired drop in blood-pressure was less after amphenone administration before the second experimental day. The decrease in basal blood-pressure may be attributed partly to a depressant effect on the central nervous system. Drowsiness, a relatively common finding accompanying amphenone administration, was noted in this patient but cleared rapidly after the drug was withdrawn.

Sodium retention and decreased urine volume following the administration of hexamethonium to lower the blood-pressure have not been adequately explained. A possible adrenal mechanism may be responsible, at least partly. Studies are now being carried out employing amphenone to block the adrenal cortex and exclude an adrenal mechanism as far as possible. The present report indicates that there is no change in the response of the kidney to acute lowering of the blood-pressure by pharmacological means after amphenone has been given. If an adrenal mechanism is concerned in the sodium and water retention, it is apparently not influenced by amphenone administration.

The patients reported here were selected from the medical service of Westminster Hospital with their active cooperation and having as complete an understanding as was possible of the nature of the investigations to be carried out, and of the direct or indirect benefits that might accrue to them or other hypertensive patients, as the result of attempts to elucidate the change in renal function in this disease, and its modification when the blood-pressure is lowered.

We are indebted to Dr. E. W. Young, of the department of clinical investigation, Upjohn Co., Kalamazoo, Michigan, for the supply of amphenone.

Clinical Investigation Unit,
Westminster Hospital,
Department of Veterans' Affairs,
London, Ontario, Canada.

J. A. LEWIS
J. B. DERRICK
J. M. JOHNSON.

8. Hertz, R., Pittman, J. A., Graff, M. M. *J. clin. Endocrin.* 1955, **16**, 705.
9. Wesson, L. G. *Medicine*, 1957, **36**, 281.

NEW SYNDROME OF FAMILIAL NON-HÆMOLYTIC JAUNDICE

SIR,—Recently there has been considerable interest in two syndromes of familial non-hæmolytic jaundice. The first has been called Gilbert's disease or constitutional hepatic dysfunction. The second has been given various names—chronic idiopathic jaundice, Dubin-Johnson syndrome, Dubin-Sprinz syndrome.

We recently encountered a young physician who has had clinical jaundice for years. His sister and father have also been jaundiced for many years. Both he and his sister resemble the father in appearance, whereas another sister resembling the mother has never been clinically jaundiced. It was initially considered that the familial jaundice represented either Gilbert's disease or chronic idiopathic jaundice. The bilirubin levels in these subjects, however, were raised in both direct and indirect levels, eliminating Gilbert's disease as a possibility. A needle biopsy of the doctor's liver revealed normal liver tissue without the presence of the coarse granular pigment characteristic of the biopsies from patients with chronic idiopathic jaundice. It thus appears that these cases represent a new syndrome of familial non-hæmolytic jaundice.

The clinical characteristics of this syndrome resemble features of both Gilbert's disease and chronic idiopathic jaundice. Chemical and histological findings, however, separate the three entities. In the new syndrome, elevated serum-bilirubin-glucuronide levels and abnormal retention of bromsulphalein clearly distinguish the disease from Gilbert's. Only unconjugated bilirubin is raised in the serum of patients with Gilbert's disease. Excretion of iopanoic acid is normal in both. Increased serum levels of bilirubin-glucuronide, as well as unconjugated bilirubin and abnormal retention of bromsulphalein, are findings which resemble those in patients with chronic idiopathic jaundice. The absence of coarse, granular, brown-staining lipofuscin pigment and normal oral cholecystography, however, enable these diseases to be distinguished.

Department of Medicine,
University of Southern California
School of Medicine, Los Angeles.

BERNARD J. HAVERBACK
SAMUEL K. WIRTSCHAFTER.

VALUE OF ELECTROCARDIOGRAPHY

SIR,—The work of Dr. Todd (April 25) deserves our thanks because it gives a necessary caution. In 55 years' practice I have seen a great many cases of coronary-artery disease that were clinically beyond doubt, but in which the electrocardiogram remained completely normal. There are surely silent zones in the heart muscle. Only the total clinical picture of the patient, together with the E.C.G., leads to the right diagnosis.

Düsseldorf. TH. OLBERT.

HOW MANY IATRICS?

SIR,—The letter by Dr. With (Feb. 21) again raises this question,[1] and prompts me to submit a descriptive, genetically correct, term for the practice of medicine in the adolescent group—*hebiatrics*. This addition to the nomenclature I first proposed to the 4th National Conference on Health in Colleges in New York City in May, 1954.[2]

There appears to be a growing interest in classifying medical practice, not only by anatomical or pathological specialties, but by age-groups. Dr. J. Roswell Gallagher, who established a clinic for "adolescent medicine" at Harvard in 1952, has more recently written, with his colleagues, on this specialty.[3] Sir Heneage Ogilvie [4] discussed medical practice in the military age-group from 18 to 25, and labelled this field "ephebiatrics". Pædiatrics has been accepted as a specialty for a quarter of a century; geriatrics has more recently come into popular use.

1. *Lancet*, 1956, ii, 1295.
2. Proceeding of Fourth National Conference on Health in Colleges, 1955; p. 49.
3. Gallagher, R. I., Heald, F. P., Masland, R. P., Jr. *New Engl. J. Med.* 1958, **259**, 24, 74, 123.
4. Ogilvie, W. *Lancet*, 1954, ii, 395.

The age at which the adolescent outgrows his pædiatrician is debatable. A recent cartoon depicts a well-developed youth smoking his pipe and halfheartedly paging through a juvenile magazine while he waits to see his pædiatrician.

In the United States 50% of the population is below 25 years of age; 13% is between the ages of 14 and 24 years. 3 million of the latter group are in colleges and universities, where, during the school year, they are under medical supervision of college health physicians who actually are "specialising" in this area of medical practice. This situation is not unique in the United States, judging from personal observations and a review of the study of university health services made by the World University Services in 1955.

The term ephebiatrics accurately applies to medicine involving military personnel aged 18–25 years, if one is willing to include women in the original meaning of the term. Adolescent medicine correctly describes an area of practice but would not harmonise with the present terminology of specialties. The term student medicine refers only to medicine for college students. Teen-age medicine has an unhappy connotation, since one of the problems of the adolescent is his striving for maturity.

Hebiatrics leaves no doubt of its meaning. It has a sound and, like ephebiatrics, respectable origin. Hebe was the goddess of the adolescent or the young person coming up to maturity. This term fits in well with pædiatrics, geriatrics, and mesiatrics.[5] May I then offer hebiatrics as the simplest descriptive term for the practice of medicine in the adolescent groups, the age from puberty through pimples?

Student Health Service,
University of Kansas,
Lawrence, Kansas.

RALPH I. CANUTESON.

CAUSE OF CLUBBING

SIR,—It was not the intention of my letter of May 9 to cross swords with Dr. Hall about his hypothesis on the cause of finger-clubbing in cases where venous blood by-passes the alveoli. I feel there is need, however, for reappraisal of the relationship of clubbing to hypertrophic osteoarthropathy.

In cyanotic heart-disease, even with severe clubbing, osteoarthropathy is an extreme rarity,[6] whereas severe crippling osteoarthropathy associated with pulmonary disease usually occurs without cyanosis and bronchial-artery/pulmonary-artery precapillary (not pulmonary-artery/pulmonary-vein) shunts have been demonstrated in these cases. These facts suggest the operation of two distinct mechanisms, in effect, two distinct states.

I agree with Dr. Hall's suggestion about the need for water and electrolyte studies in osteoarthropathy.

Baguley Hospital,
Manchester, 23.

LESLIE DOYLE.

ARTERIAL SPASM FOLLOWING INTRA-ARTERIAL INJECTION OF THIOPENTONE

SIR,—The interesting article by Professor Burn and Miss Hobbs (May 30) emphasises the fact that, unlike thiopentone, hexobarbitone has never caused a vascular accident.

When thiopentone was introduced in 1936, the virtues of hexobarbitone were largely overlooked in the enthusiasm for the new drug. A search of the literature has failed to reveal a vascular accident caused by hexobarbitone, nor does it cause damage to tissue when injected perivenously or in the region of the median nerve. The introduction of a 2·5% solution has not entirely removed this danger with thiopentone.

The incidence of spasm of the larynx under hexobarbitone anæsthesia has been shown to be a quarter of that under thiopentone. From the point of view of the patient the speed of induction of anæsthesia is the same with both drugs. In over 20 years' experience with hexobarbitone, the textbook complication of sneezing during induction has never been encountered. With the almost universal use of muscle-relaxant drugs, it is unnecessary to rely on the deep anæsthesia produced by thiopentone, and a "sleep dose" of hexobarbitone produces a much smoother anæsthesia than a similar dose of thiopentone. It would seem that in these days, when the ever-present threat of litigation looms over the anæsthetist, the use of hexobarbitone has much to recommend it.

London, W.1. MASSEY DAWKINS.

5. Vakil, R. J. *ibid.* 1956, ii, 1310.
6. Trever, R. W. *Ann. intern. Med.* 1958, **48**, 660.

BOXING

SIR,—Your leader shows little sense of proportion and verges on the hysterical. On the same day it was published there was an account in the papers of yet another public-school boy dying from cerebral hæmorrhage caused by a cricket ball. And so it goes on. Cricket should be abolished by law!

The bulk of boxing in this country takes place in hundreds of schools and clubs to the great advantage of a host of young men and boys. It is a splendid and exciting way of getting exercise almost anywhere and with a minimum of equipment. Every muscle in the body comes into play, and with them the mind and the endocrines. "This is the worst moment in my life," said Julian Grenfell to Kingsley Fairbridge when they were waiting to fight in the final of the heavyweights of the Oxford and Cambridge contests. One went on to get the V.C., the other in face of every difficulty to found the glorious Fairbridge Schools. Courage and endurance are qualities that have to be trained for, and boxing is an excellent medium for that training.

I lived for seven years in a Boys' Club in Hoxton, we boxed at least twice a week, and in that time the only injury that was not trivial was one broken nose. Nineteen-twentieths or more of boxing is practice, but even in competitions the chances of being hurt seriously compare favourably with rugger and mountaineering, which after the Whymper disaster on the Matterhorn Queen Victoria wanted to abolish by law. The London inter-hospital boxing competitions for medical students have been going on for over fifty years now and are vigorous affairs. How many cases of permanent harm from them can you produce? Any? If these young people, as you propose, were not allowed to box, what do you suppose they would do with their energies? A few more would get their excitement from teddy-boy gangsterism and ploys of the "breaking and entering" type, some who could afford it from racing cars and motor-bikes which are infinitely more lethal than boxing, most would seek to test their incipient manhood against any risk that chanced their way. Or do you think they would sit still and knit?

I hold no brief for professional boxing, which is primarily a money matter, nor do I approve of small boys boxing as they do in some preparatory schools; they don't enjoy it and their skulls are not fit for it. But leave the bulk of boxing, amateur boxing, alone.

Beckley, Rye. C. G. LEAROYD.

SIR,—In your leading article last week you ask for the abolition of the Noble Art—a suggestion which I and many other people would strongly oppose. Boxing teaches a man to stand up to the physical and moral stresses of life while fighting under stringent rules of combat. It is, of course, a hard game, but is not life itself beset with far more dangers as well as other forms of sport both amateur and professional? The evidence you give points to more stringent medical supervision of both amateur and professional boxing and directives to referees

and judges to stop the bout if a contestant is knocked down twice in a fight or appears dazed while on his feet over a period of thirty seconds. In my long association with the ring I have never come across any of the cases you cite and I have had my share of punches in many fights.

Tunbridge Wells. E. F. ST J. LYBURN.

THE PROTRUDED DISC

SIR,—The statement in your annotation of May 16 that wide laminectomy is essential to success in the surgical treatment of protruded lumbar intervertebral disc lesions is mistaken. Wide laminectomy with removal of vertebral spines must inevitably weaken the back and if the articular processes are damaged there will be a tendency to stiffness. Thus the patient may be left with a weak stiff back, while the aim of aftercare should be to produce a strong mobile back.

To obtain a view of the whole of one half of a disc space it is only necessary to make a small opening into the spinal canal by removing the lower margin of the lamina above with its underlying piece of ligamentum flavum. Through such an opening any sizable lateral disc protrusion will present immediately. Also by this means the vertebral spines are left intact and the sacrospinalis muscle need be separated and retracted on one side only. If necessary two or more disc spaces may be explored in this way without weakening the bony structure or depriving muscle of bony attachments. Limited opening of the spinal canal has the additional advantages that it is easier to obtain a bloodless field and postoperative discomfort is reduced. Rather than being advocated, formal laminectomy should be reserved for giant disc and central disc protrusions, both of which are relatively uncommon.

London, W.1. R. CAMPBELL CONNOLLY.

PERIODIC MIGRAINOUS NEURALGIA OF WILFRED HARRIS

SIR,—Dr. Bickerstaff's paper (May 23) about the Periodic Migrainous Neuralgia of Wilfred Harris is excellent, and I agree with almost everything in it. It may be of interest, however, that I wrote on the same subject 12 years ago,[1] when I proposed the name Harris-Horton disease for this special kind of headache. I emphasised that attacks of headache appeared in bouts of 4-8 weeks and that no treatment can be properly evaluated without knowledge of this periodicity. I reported good results with ergotamine tartrate given regularly two or three times a day during the bouts of pain. In the last few years I have usually given ergotamine suppositories instead of tablets.

Department of Neurology,
University of Uppsala, Sweden. K. A. EKBOM.

TRACHEAL FENESTRATION

SIR,—I read with great interest the letter by Dr. Mayer in your issue of Feb. 28. In a letter in the *Journal of the American Medical Association* of Jan. 3 last I explained the chronological history of this operation. In fact only 2 of the first 17 cases of tracheal fenestration were under the care of Dr. Mayer and Dr. Rappapot.

To eliminate confusion on the subject, may I state the main indications for tracheal fenestration, based on our experiences with 26 cases:

(1) Excessive tracheobronchial secretions associated with pulmonary insufficiency.

(2) Pulmonary insufficiency due to advanced emphysema, either wet or the so-called " dry " variety (with or without cor pulmonale, even when in cardiac failure).

8 of our first 24 patients with severe pulmonary insufficiencies have been rehabilitated. The rest improved to varying degrees. The operative mortality is zero. These facts and the detailed observations of those who have been in contact with these patients and followed them closely after their discharge from hospital can correct the erroneous statements made by Dr. Mayer.

New York. E. E. ROCKEY.

1. Ekbom, K. A. *Acta psychiat., Kbh.* 1947, suppl. 46, 106.

SALICYLAZOSULPHAPYRIDINE IN CHRONIC SKIN SEPSIS

SIR,—In 1955 Schoch and McCuistion [1] described the use of salicylazosulphapyridine (' Azulfidine ') in chronic skin conditions. With a dose of 2–4 g. daily for one to sixteen weeks they felt the drug was beneficial in over half their 68 cases of various dermatoses. They found it valuable for the control of pustular acne, perhaps because it had the specific action on connective tissue claimed by Bargen. 3 of their cases showed intolerance (nausea, diarrhœa, and generalised eczematous dermatitis medicamentosa respectively) to the drug sufficient to cause its withdrawal. Schoch and McCuistion quote the Karolinska Institute in Stockholm as treating 800 cases without serious side-reactions.

Although the drug was not apparently in general use in England in 1955, regular supplies were obtained from Stockholm, and in this clinic it has been much used for the past $3^1/_2$ years. We have confirmed the usefulness of the drug, especially for pustular acne and infected skin conditions.

The dosage preferred has been only 0·5 g. t.d.s., but always continued for a minimum of three months in chronic conditions and often for a year or more. At first periodic differential leucocyte-counts were performed, but later the patient was simply given a notice urging him to report immediately if he developed a sore throat or unexplained illness. No serious toxic effects were encountered and the drug is almost invariably tolerated well. A man of 37 with gangrenous ulceration of the leg and anæmia, who had ulcerative colitis of which he was unaware but which was demonstrated by sigmoidoscopy, was unable to tolerate high doses (6 g. daily) which made him feel ill.

Spriggs et al.[2] described 3 cases of toxic Heinz-body anæmia due to this drug, and mentioned a 4th case in an addendum. 3 of these patients had ulcerative colitis and the other a malabsorption syndrome due to ileocolic fistula. Methylviolet is required to demonstrate this red-cell abnormality which does not show with Romanowsky stains.

Since studying their report a list was made of the next 25 patients attending this skin clinic who had been prescribed salicylazosulphapyridine. After three months on the drug (1·5 g. daily) search was made for Heinz bodies. The method of search for these bodies was their method [1] (as described by Dacie).[3] The 25 cases comprised pustular acne (17), chronically infected seborrhœic eruptions (5), pustular rosacea (1), dermatitis repens (1), and chronic non-tuberculous granulomatous abscesses of buttocks, secondary to ischiorectal abscesses (1). None of these cases showed Heinz bodies after a three-month course, and 9 have been under continuous treatment with the drug for six months or more without formation of Heinz bodies. Anæmia was not a feature of any case, and the lowest hæmoglobin was 11·8 g. per 100 ml. (80%).

Salicylazosulphapyridine is confirmed as a particularly effective and non-toxic sulphonamide for dermatological use. 0·5 g. t.d.s. is tolerated well for months on end and has produced no Heinz-cell bodies in the 25 cases for which search has been made. Probably Heinz-cell formation is a manifestation of high doses, as are recommended, for instance, for ulcerative colitis. Anæmia,

1. Schoch, E. P., McCuistion, C. H. *J. invest. Derm.* 1955, **25**, 123.
2. Spriggs, A. I., Smith, R. S., Griffith, H., Truelove, S. C. *Lancet*, 1958, i, 1039.
3. Dacie, J. V. Practical Hæmatology; p. 76. London, 1956.

however, is a frequent finding in ulcerative colitis and it may be that with this condition the red cells are more easily damaged by salicylazosulphapyridine.

Department of Dermatology,
The Royal Infirmary, Sunderland. P. INMAN.

NON-HYPOCHOLESTEROLÆMIC ACTION OF NICOTINIC ACID IN DOGS

SIR,—We have previously reported [1] the inefficacy of daily doses (1–4 g.) of nicotinic acid by mouth in lowering serum-cholesterol concentrations in dogs. Recently Sodi-Pallares et al. reported [2 3] that in dogs receiving 50 mg. of nicotinic acid by mouth daily, serum-cholesterol concentration was reduced by 21–26%. We have been unable to confirm their results.

In long-term studies with large doses of nicotinic acid 1 male and 2 female mongrel dogs were used. The dogs were housed in separate cages in a constant-temperature air-conditioned room, and received a diet of horse meat and commercial dog food. The methods of Furman et al.[4] were used for analysis of serum and tissue.

The results from 1 dog, which are representative of the studies in the other 2 animals, are given in table I. The increase in total cholesterol from a control level of 94 mg. per 100 ml. to 103 mg. per 100 ml. for the second treatment course is significant ($P < 0.01$), but may be related to the laparotomy which was performed to obtain a liver biopsy immediately preceding the second control period. This is the only statistically significant difference in different sequential periods.

The liver-biopsy specimen taken immediately following the first course of nicotinic acid was unremarkable histologically and histochemically. Lipid analysis revealed: total lipids 42·3, cholesterol 2·45, and lipid P 0·92 mg. per g. wet weight (all values being within normal ranges for dogs as determined in this laboratory).

Results from 4 dogs given 50 mg. of nicotinic acid by mouth daily in an experiment similar to that reported by Sodi-Pallares et al.[2] are given in table II. These results show a complete lack of effect of nicotinic acid on the serum lipids and lipoproteins studied. The difference between our findings and those of Sodi-Pallares et al. may be correlated in some way with the higher levels of cholesterol reported by them for the control periods (200–275 mg. per 100 ml.).

Our data show that the dog is refractory to doses of nicotinic acid which lower serum-cholesterol in man. Thus it seems that the metabolic interrelationship between nicotinic acid and cholesterol is different in the dog from those in man and the rabbit.

L. N. NORCIA
Oklahoma Medical Research Foundation and University of Oklahoma, Oklahoma City, U.S.A. H. J. BROWN
R. H. FURMAN.

1. Norcia, L. N. American Society for the Study of Arteriosclerosis, Chicago, November, 1957.
2. Comesana, F., Nava, A., Fishleder, B. L., Sodi-Pallares, D. *Amer. Heart J.* 1958, **55**, 476.
3. Nava, A., Comesana, F., Lozana, Elena, Fishleder, B. L., Sodi-Pallares, D. *ibid.* 1958, **56**, 598.
4. Furman, R. H., Norcia, L. N., Robinson, C. W., Gonzalez, I. E. *Amer. J. Physiol.* 1957, **191**, 561.

TABLE I—SERUM-LIPID AND LIPOPROTEIN VALUES IN A 20 KG. ADULT MALE DOG RECEIVING NICOTINIC ACID BY MOUTH (MEAN VALUES AND STANDARD ERRORS OF MEANS)

Treatment sequence	Total cholesterol (mg. per 100 ml.)	Ester cholesterol %	Lipid P (mg. per 100 ml.)	Lipoproteins (mg. per 100 ml.)	
				$-S_{f\,1-21}$ 0-20 "alpha"	$-S_{f\,1-21} > 20$ "beta"
Control period 5 weeks; 5 serum samples * ..	100±3	75±1	10·1±0·4	429±16	58±10
1st course nicotinic acid (1–4 g. per day (6 × wk) for 3 months; 8 serum samples * ..	97±5	73±1	9·5±0·3	417±15	49±10
Control period 3 months; 5 serum samples * ..	94±2	73±1	9·3±0·1	433 (single anal.)	42 (single anal.)
2nd course nicotinic acid 1–4 g. per day (6 × wk) for 7 months; 14 serum samples *	103±2	76±1	9·6±0·1	413±9	49±4
Control period 6 days; 4 serum samples * ..	99±2		9·3±0·2		

* Total cholesterol and lipid P were determined on all serum samples obtained. Unesterified cholesterol and lipoproteins were determined on about half the serum samples obtained.

TABLE II—SERUM-LIPID VALUES IN DOGS RECEIVING 50 MG. DAILY OF NICOTINIC ACID BY MOUTH

Period	Date	Total cholesterol (mg. per 100 ml.)				Lipid P (mg. per 100 ml.)			
		Dog 71	Dog 73	Dog 74	Dog 75	Dog 71 21 kg. ♂	Dog 73 17 kg. ♀	Dog 74 26 kg. ♂	Dog 75 17 kg. ♀
Before treatment	Oct. 28, 1958	124	132	144	200	11·7	12·4	14·3	16·5
	,, 29, ,,	124	134	146	199	12·0	12·5	14·0	16·4
	,, 31, ,,	120	128	139	183	11·9	12·9	13·9	17·3
	Nov. 3, ,,	127	143	147	221	12·3	13·4	14·0	18·5
	Nicotinic acid began Nov. 3, 1958								
During treatment	Nov. 4, 1958	131	126	164	185	12·8	12·4	14·5	17·1
	,, 5, ,,	121	132	147	206	12·7	12·8	14·2	17·7
	,, 6, ,,	122	126	143	196	12·1	12·3	14·0	17·1
	,, 7, ,,	129	122	146	204	12·9	12·5	14·3	17·5
	Nicotinic acid discontinued Nov. 7, 1958								
After treatment	Nov. 14, 1958	126	124	146	208	12·0	11·9	13·9	16·8
	Dec. 17, ,,	138	162*	143	166	13·2	14·5*	13·9	15·2

* Dog in œstrus.

MURDER AT THE CROSS-ROADS

SIR,—Dr. Geiringer's paper has drawn vigorous and able comment from Dr. Clyne and Dr. Fry (May 30). Certainly his picture of the average general practitioner seems to be a product of his own fantasy, and it is not surprising that he gives no account of what practical survey he undertook as a basis for his study. A paper on a clinical topic so devoid of validation would hardly find a publisher.

On the subject of the hospitalisation of medicine he has raised an issue that needs debate. The elaboration of techniques has made some part of this hospitalisation inevitable and desirable. No doubt also the economic pressure of capitation payment is partly responsible. But surely a major factor is the tendency of many consultants, as their work becomes more specialised and remote from general practice, to look on general practitioners as permanent undergraduates. The recent correspondence about the Tavistock Clinic courses in psychological problems in general practice is pertinent.

At first modestly called research seminars, these courses have now been running for ten years and nearly two hundred general practitioners have undertaken them. I doubt if one of this number would disagree with the testimonies you have published to their unique value in the everyday conduct of general practice, apart from the more specialised object of acquiring skill in psychotherapy. The consultants of the Tavistock Clinic have deliberately abandoned the lecturer's rostrum to sit as equals in discussion with their general-practitioner colleagues, to learn as well as to teach. This is post-graduate training of the highest order, dealing with *the* basic technique of general practice—the understanding and treatment of patients as human beings in the setting of their lives, their homes, and their families. Yet the decision of a small committee, presumably of consultants, is that this training is unworthy of official recognition (and consequently of the expenditure of public money)—a decision taken, I believe, with no inquiry among those with actual experience of the training. It cannot be healthy either for hospital medicine or for general practice that the opinions of such a substantial body of general practitioners should be ignored in this matter.

Bromley, Kent. V. J. MARMERY.

Parliament

Mental Health Bill in the Lords

THE sincerity of the welcome which Noble Lords offered this Bill, when the LORD CHANCELLOR moved its second reading on June 4, was all the clearer because their appreciation was mixed with thoughtful criticisms. The debate ranged over most of the controversial points which have been raised in our own correspondence columns and elsewhere during the Bill's parliamentary progress. Their main concern was lest the Act should not fulfil the promise of the Bill for lack of money, staff, research, and buildings. As Lord TAYLOR pointed out, "reform of the law is a comparatively cheap form of reform, but reform of the Mental Health Service is going to be a very costly business". Lord COHEN OF BIRKENHEAD, too, stressed the wide gap "between what we need and what we have".

Other speakers mentioned the continuing shortage of psychiatrists, and the need for many more social workers to which the Younghusband report has once more lately drawn attention. With these shortages is bound up the problem of training, and Lord AMULREE suggested that many mental welfare officers, for instance, would need more training, to meet the greater responsibilities which the Bill would impose on them. He was also anxious that medical students should be given more opportunity to study mental disorders in out-patient departments and observation wards, for it was this kind of experience which would help general practitioners to share in the domiciliary care of mental patients.

Noble Lords shared the general regret that the local authorities' powers to provide welfare, aftercare, and domiciliary services for the mentally ill had not been made mandatory. Lord SILKIN agreed that the Minister of Health by issuing directions would go a long way towards making them mandatory without actually mentioning it in the Bill, but he wondered how effective this circumlocutory device would in fact prove. Lord TAYLOR doubtfully recalled the lack of enthusiasm and the parsimony with which many local authorities had run their health services in the past, and hoped that the regional hospital boards would not be deprived of the power to continue providing aftercare. Lord STONHAM pointed out that the local-authority health officers and the hospitals would have to work together on almost every case and thought that it would be wiser to make the hospitals not only joint partners but also prime movers in these domiciliary schemes.

Criticisms of the part of the Bill dealing with compulsory admissions centred on the disappearance of the justice of the peace and on the definition of psychopathic disorder. Baroness WOOTTON OF ABINGER drew these related topics together. She regretted the abolition of the magistrates' consent for compulsory treatment, for she thought that there was today a tendency to endow the medical man with some of the attributes of the medicine man. This sometimes placed doctors in an invidious position and sometimes possibly laid them open to the exercise of powers which the public would regard as arbitrary in others. The creation of the new category of psychopaths was, in her view, one stage in an important social development characteristic of our age—the encroachment of medicine into the province which was formerly reserved for morals. This encroachment, she suggested, first made itself felt in the Homicide Act, 1957, when diminished responsibility became a defence in charges of murder, making it possible for the charge to be reduced to one of manslaughter. It was now carried a stage further, inasmuch as the psychopath was not so much given a legal defence on the ground of his psychopathy as enabled to bypass the courts altogether. The definition of psychopathy in the Bill would cover practically the whole of the recidivist population. If we were coming to a time when all serious and persistent antisocial conduct was held to be a medical problem, and only occasional or less serious antisocial conduct was thought to be a matter for penal treatment, we would get a very odd selection of cases in the courts and some strange consequences. She thought that there might be much to be said for this development. Penal treatment in the courts had not been such a success that we had no cause to try something else. But she felt that it was important to call attention to the fact that the creation of this category of psychopaths was not just a little trimming of our present legal and judicial procedure. It was the herald of a profound and far-reaching revolution.

QUESTION TIME

Threshold for Radiation Damage

Mr. ANEURIN BEVAN asked the Prime Minister if he would give the most recent evidence on the question of whether there was a threshold value for exposure to radiation below which there was no risk of genetic damage, leukæmia, or bone cancer.

Mr. HAROLD MACMILLAN replied that, on the existing evidence, it was impossible to say whether or not there was a threshold dose of radiation—from whatever source, natural or man-made. There was some recent evidence to suggest that the genetic effects on mice of exposure to low doses of radiation might be less than would be expected on previously accepted assumptions. As for the somatic effects, although it was easy to demonstrate by experiment the harmful effects following high doses it was very difficult to demonstrate any effects after exposure to very low doses of the order occurring in human bones from fallout.

To a suggestion of Mr. Bevan's that the threshold was a fake concept from the beginning, Mr. Macmillan replied that the Medical Research Council and the United Nations Scientific Committee had always accepted that there was no threshold of radiation exposure below which it could be said with certainty that no genetic damage occurred. As for somatic effects, it was much more difficult to answer exactly, and that was why both the U.N. Committee and the M.R.C. had always tried to give calculations including upper and lower limits.

Obituary

GEORGE MATTHEW FYFE

C.B.E., M.B. Aberd., F.R.C.P.E., D.P.H.

Dr. G. Matthew Fyfe, medical officer of health for Fife, died at his home at Cupar on June 2 at the age of 64.

He was born in Aberdeen and was a son of the school-house. He was educated at Robert Gordon's College and Aberdeen University. During the first year of the 1914–18 war he served in the Gordon Highlanders and he was seriously wounded at Loos. Later he acted as assistant in the pathological laboratory of the First Scottish General Hospital. Soon after graduating M.B. in 1920 he was appointed Carnegie research assistant in the physiology department of Aberdeen University and assistant medical officer of the general medical and cardiac clinic of the Ministry of Pensions in Aberdeen. In 1923 he became assistant M.O.H. for Aberdeen, and in 1926 he moved to Fife as M.O.H. for St. Andrews and as bacteriologist to the James Mackenzie Institute for Clinical Research. He became deputy M.O.H. for Fife in 1930, and in 1938 he took over as county medical officer.

He was appointed to the first Scottish Health Services Council, and he was also a member of the Scottish Water Advisory Committee in 1946, and of the Scottish Food Hygiene Council in 1956. He served for many years on the Scottish Mental Health Subcommittee, and the Fertilisers and Feeding Stuffs Advisory Committee. In 1953 he was elected F.R.C.P.E., and he was appointed C.B.E. three years later.

A colleague writes:

"On his appointment in 1938 the major task facing Matthew Fyfe was the organisation of the county war-time emergency medical services. With the end of the war in sight his interests and great energies turned to other problems, notably housing, infant mortality, and child health. The National Health

Service brought a new challenge, and in the welfare services he found fresh outlets for his enthusiasm. In particular he pushed ahead with vigour and understanding the development of services for the elderly. But he always remained a great sanitarian—housing, water-supply, drainage, safe milk, and clean food were his constant preoccupations. Of late years his attention had turned increasingly to the problem of mental health and the welfare of the handicapped and to the establishment of a climate of opinion favourable to his far-sighted proposals.

"A big man physically and of distinguished appearance, he was at all times a commanding, and often at first meeting a formidable, personality. He suffered fools impatiently and preferably not at all, but accepted without question responsibility for every act of a subordinate—a characteristic which endeared him to even the most wayward. Life in his department was often hectic, sometimes a little precarious, but never boring, and his overflowing vitality and energy communicated itself to all about him."

Dr. Matthew Fyfe leaves a widow and three sons.

Diary of the Week

JUNE 14 TO 20

Monday, 15th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Psychiatric Aspects of Epilepsy.
INSTITUTE OF NEUROLOGY, The National Hospital, Queen Square, W.C.1
5.30 P.M. Dr. W. Ritchie Russell: Rehabilitation in Diseases of the Nervous System.

Tuesday, 16th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Sir Macfarlane Burnet: Autoimmune Disease—(a) Modern Immunological Concepts. (First of two Croonian lectures.)
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Mr. A. K. Monro: Malignant Melanoma.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. E. H. Larkin: Ataractic, Euphoriant, and Psychotropic Drugs.

Wednesday, 17th

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Henry Haber: The Dyskeratoses.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. J. R. Belcher: Re-stenosis of the Mitral Valve.

Thursday, 18th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Sir Macfarlane Burnet: Autoimmune Disease—(b) Pathology of the Immune Response. (Second of two Croonian lectures.)
POSTGRADUATE MEDICAL SCHOOL
4 P.M. Prof. C. E. Dent: Hartnup Disease, an Inborn Error of Metabolism.

Friday, 19th

POSTGRADUATE MEDICAL SCHOOL
10 A.M. Prof. David Slome: Experimental Studies on Wound Healing.
FACULTY OF RADIOLOGISTS
4.30 P.M. (Royal College of Surgeons, Lincoln's Inn Fields, W.C.2.) Prof. W. V. Mayneord: Problems in the Metabolism of Radioactive Materials in the Human Body. (Skinner lecture.)
BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
11.30 A.M. Radiobiology meeting.

Appointments

ARMSTRONG, F. C., M.B. St. And.: assistant M.O. and school M.O., Wortley, near Sheffield.
ROYDE, C. A., M.D. Lond., D.P.H.: senior M.O. (nursing services division), Manchester.

Manchester Regional Hospital Board:

ATKINSON, D. W. J., M.D., M.S. Lond., F.R.C.S.: part-time consultant neurosurgeon, Crumpsall, Booth Hall, and Prestwich hospitals.
LONSDALE, W. H., M.B. Manc., F.R.C.S.: part-time consultant surgeon, Preston and Chorley group of hospitals.
YOUNG, K. D., M.D. Edin., M.R.C.P.E.: part-time consultant chest physician, Lancaster and Kendal hospitals.

Births, Marriages, and Deaths

BIRTHS

BROADHEAD.—On May 1, to Jill (née Moody), wife of Dr. H. H. Broadhead, of Newport, I.O.W.—a son.

DEATHS

HUGHES.—On May 30, George Sydney Norman (Peter) Hughes, D.S.O., L.M.S.S.A., colonel, R.A.M.C., of Birchgrove, Trawscoed, Cards, aged 51.

Notes and News

NEW DEPARTMENTS AT THE RADCLIFFE

To mark the completion of four new departments at the Radcliffe Infirmary, Oxford, the Vice-Chancellor of the University and the chairman of the board of governors of the United Oxford Hospitals gave a luncheon at Rhodes House on June 5. The new departments are the Nuffield departments of surgery and medicine, the laboratories of the regius professor of medicine, and the X-ray department. Though medicine was one of the first five regius chairs founded at Oxford in 1546, the Vice-Chancellor, Mr. T. S. R. Boase, owned that the great epoch of Oxford medicine really began in 1936 when Lord Nuffield's benefaction made possible a completely new conception of what medical studies might be in Oxford.

Replying to the Vice-Chancellor's toast of The Guests, Sir Harold Himsworth, secretary of the Medical Research Council, saw the occasion as an identifiable turning-point in the history of medicine at Oxford: the first stage was now complete in providing Oxford with the material facilities for the complete study of medicine and biology. The development of techniques of investigation that could safely be applied to man had been one of the advances that had helped to bridge the intellectual disparity between the preclinical and clinical branches of medicine, so that it was now possible to treat the whole of medical knowledge as one continuum. Knowledge of the normal and abnormal were indissolubly linked, and it was only through their interaction and synthesis that the full potentialities, both intellectual and practical, of the study of living organisms could be realised. In this, Sir Harold declared, lay the essential significance of the present occasion. Lord Nuffield could be in no doubt about the effectiveness of his prescience: his dream had been translated into action and would now be woven into the stuff of other men's lives.

WORLD HEALTH ORGANISATION

IN his closing address to the Twelfth World Health Assembly in Geneva on May 29, Sir John Charles, the president, outlined the achievements of the three-week session and paid tribute to the generosity of Switzerland and the Canton of Geneva for their offered loan towards the cost of the new W.H.O. headquarters. He welcomed the increasing emphasis on research in W.H.O., but pointed out that work planned for the future was only a small contribution to that already in progress. Sir John Charles continued: "But if our contribution is of a special kind, if it seeks to fill in some of the gaps in communication and coordination, if it prospects some of the outstanding and uninvestigated problems more particularly pertaining to public health, if in brief it acts as a catalyst, then it will have an influence altogether greater than its endowment, and the value of its assistance will be out of all proportion to the budget it will deploy."

The Assembly had earlier unanimously approved a resolution designed to retain Dr. M. G. Candau as director-general of W.H.O. until July, 1963. Dr. Candau is to announce his decision before Nov. 1, 1959, and, if he accepts, will have served two five-year terms by the end of his appointment.

The Assembly also discussed the eradication of malaria and of smallpox. The total cost of eradicating malaria from the world is estimated at 1691 million dollars, and in most countries an average of eight years would be required. Already 10, and possibly 13, of the species of mosquito which carry malaria are resistant to present-day insecticides, and it is urgent to achieve eradication before these become completely ineffective. Several delegates declared that obstacles to the eradication of malaria were apathy and ignorance besides financial and administrative difficulties. As regards smallpox, although vaccination has been known for over a hundred and fifty years, more than 200,000 cases were reported in Asia last year. Mass vaccination in the field would be made easier by the recently introduced freeze-dried vaccine, and would be relatively cheap at an estimated cost of 100,500 dollars per million people.

The Executive Board of W.H.O., which met on June 1 and 2 under the chairmanship of Prof. E. J. Aujaleu (France),

reviewed B.C.G. vaccination programmes. Between 1951 and 1958, 88 million people were given B.C.G.; and a preliminary report had showed the degree of protection was about 80%, and that mass vaccination entailed few risks and could be made acceptable to large populations.

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names:

Approved name	*Other names*
Benzethidine	Ethyl 1-(2-benzyloxyethyl)-4-phenylpiperidine-4-carboxylate
Bretylium Tosylate	*N-o*-Bromobenzyl-*N*-ethyl-*NN*-dimethylammonium tosylate (Tosylic acid is adopted as the trivial name for *p*-toluenesulphonic acid)
	Darenthin
Dichlorphenamide	1:2-Dichloro-3:5-disulphamoylbenzene
	Daranide
Diprophylline	7-(2:3-Dihydroxypropyl)-theophylline
	Isophylline; Neutraphylline; Silbephylline
Furethidine	Ethyl 1-(tetrahydrofurfuryloxyethyl)-4-phenylpiperidine-4-carboxylate
Imipramine	1-(3-Dimethylaminopropyl)-4:5-dihydro-2:3-6:7-dibenzazepine
	Tofranil is the hydrochloride
Iodipamide	*NN'*-Adipoylbis (3-amino-2:4:6-tri-iodobenzoic acid)
	Biligrafin is the bis-*N*-methylglucamine salt; Endografin is the bis-*N*-methylglucamine salt
Metaraminol	(-)-2-Amino-1-*m*-hydroxyphenylpropan-1-ol
	Aramine is the hydrogen (+)-tartrate
Methocarbamol	2-Hydroxy-3-*o*-methoxyphenoxypropyl carbamate
	Robaxin
Methotrexate	4-Amino-10-methylpteroylglutamic acid
	Amethopterin
Phanquone	4:7-Phenanthroline-5:6-quinone
	Entobex
Phenelzine	Phenethylhydrazine
Phenglutarimide	α-2-Diethylaminoethyl-α-phenylglutarimide
	Aturbane is the hydrochloride
Sulphadimethoxine	6-*p*-Aminobenzenesulphonamido-2:4-dimethoxypyrimidine
	Madribon

Proprietary name	*Approved name reference*
Amethopterin	Methotrexate
Aramine	Metaraminol
Aturbane	Phenglutarimide
Biligrafin	Iodipamide
Daranide	Dichlorphenamide
Darenthin	Bretylium Tosylate
Endografin	Iodipamide
Entobex	Phanquone
Isophylline	Diprophylline
Madribon	Sulphadimethoxine
Neutraphylline	Diprophylline
Robaxin	Methocarbamol
Silbephylline	Diprophylline
Tofranil	Imipramine

University of Cambridge

On May 30 the following degrees were conferred:

M.D.—*T. S. Leeson, G. C. Manning, R. O. Murray, I. B. Smith.
M.B., B.Chir.—*L. J. Bishop.
M.B.—J. M. Stephenson.

* By proxy.

University of London

Mr. A. J. H. Rains, senior lecturer in the University of Birmingham, has been appointed to the chair of surgery at Charing Cross Hospital Medical School.

Mr. Rains, who is 38 years of age, was educated at Christ's Hospital School and qualified from St. Mary's Hospital, London, in 1943. After holding house-appointments at Park Prewett Hospital he served with the R.A.F. Medical Service and later was a supernumerary registrar at St. Mary's Hospital and resident surgical officer at Bedford County Hospital. He took the F.R.C.S. in 1948 and M.S. in 1952. He has held his present appointment in Birmingham since 1954, and he is also surgeon to the United Birmingham Hospitals. His published work includes papers on surgery of the gallbladder, the treatment of inguinal hernia, and the surgery of arteries.

Dr. G. R. F. Hilson, senior lecturer at St. George's Hospital Medical School, has been appointed to the readership in bacteriology at that school.

On April 20 the degree of M.D. was conferred on P. W. Darby and J. D. Pollitt.

At recent examinations for the D.P.M. the following were successful:

J. S. Bearcroft, A. A. Black, L. J. Clein, B. M. Davies, C. J. Wardle.

University of Birmingham

Prof. Dugald Baird has been appointed Ingleby lecturer for 1960, and Prof. J. Z. Young William Withering lecturer for 1960.

Royal College of Physicians of London

On Tuesday and Thursday, June 23 and 25, at 5 p.m., at the college, Pall Mall East, S.W.1, Prof. J. F. Brock will give the Humphry Davy Rolleston lectures. His subject will be nutrition and the clinician.

Royal College of Surgeons in Ireland

At a meeting of the college on June 1, the following officers were elected:

President, Mr. T. G. Wilson; vice-president, Mr. S. F. Heatley; council, Mr. R. Atkinson Stoney, Mr. J. F. Devane, Mr. A. A. McConnell, Mr. T. O. Graham, Mr. William Doolin, Mr. Frederick Gill, Mr. A. B. Clery, Mr. Ian Fraser, Mr. M. P. Burke, Mr. E. N. McDermott, Mr. J. H. Coolican, Mr. T. A. Bouchier-Hayes, Mr. N. A. Kinnear, Mr. D. J. Riordan, Mr. J. P. Lanigan, Mr. F. A. Duff, Mr. Douglas Montgomery, Mr. J. M. McAuliffe Curtin, Mr. Eoin O'Malley.

Oliver Bird Prize

This prize for 1958 has been awarded to Prof. M. C. Shelesnyak of the Weizmann Institute of Science, Israel, for his work on the role of histamine in the decidual response of the endometrium and the discovery that ovum-implantation can be suppressed by the presence of histamine antagonists in the uterus before nidation.

Royal Commission on Remuneration

The Royal Commission on Doctors' and Dentists' Remuneration have ended their hearings of evidence in public. Anyone who wishes to submit further written evidence should do so not later than June 30. The address of the Commission is 10, Carlton House Terrace, London, S.W.1.

Dental Health Education in Scotland

The Secretary of State for Scotland has set up a standing committee on dental health education. The medical members of the committee are: Prof. John Boyes, Dr. T. H. J. Douglas, Dr. Bryce Nisbet, Dr. J. Riddell, and Dr. J. L. Trainer.

European Congress of Allergy

This congress will be held in London from Sept. 1 to 4. Further particulars may be had from Dr. A. W. Frankland, Wright-Fleming Institute of Microbiology, St. Mary's Hospital, London, W.2.

Presentation to Sir Landsborough Thomson

On May 25 Sir Landsborough Thomson, who has retired after some forty years' service with the Medical Research Council, was presented with his portrait. The presentation was made by the Earl of Limerick, chairman of the Council. Sir Henry Dale, Sir Harold Himsworth, and Mr. Peter Scott, who painted the portrait, also spoke.

The Problem of Guilt

The National Association for Mental Health has invited clergy to a meeting on this subject at 2 p.m. on Wednesday, June 17, at 1, Wimpole Street, London, W.1. The speakers will be Father Thomas Gilby and Dr. Edward Glover. Further particulars may be had from the education secretary of the Association, 39, Queen Anne Street, W.1.

Society for Relief of Widows and Orphans of Medical Men

The report of this society for 1958 shows that the membership stands at 147. At the end of the year 23 widows and 2 orphans were in receipt of grants. During the year the society distributed £4000, including £2500 from the Brickwell fund. At the end of the year the market value of the society's investments was £117,000, and during the year £2000 savings bonds 3% 1960/70 were bought. The president is Sir Robert Young, and the address is 11, Chandos Street, London, W.1.

The honorary degree of doctor of laws has been conferred by the Rockefeller Institute on Lord Adrian.

Prof. B. G. Maegraith has been appointed honorary civil consultant in tropical hygiene to the Royal Air Force.

The offices of the Royal Medical Benevolent Fund have been moved. The address of the Fund is now 37, St. George's Road, Wimbledon, London, S.W.19.